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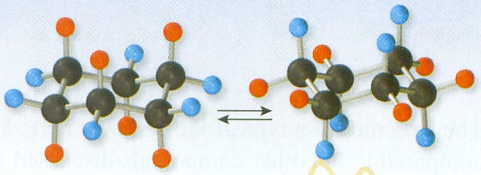

Stereochemistry I

CIS–TRANS ISOMERS AND CONFORMATIONS

CHAPTER 6

MASTERING ORGANIC CHEMISTRY

- Recognizing Cis–Trans Isomers and Estimating Their Relative Stabilities
- Designating the Configuration of Cis–Trans Isomers
- Determining Conformations about Single Bonds and Estimating Their Relative Energies
- Understanding the Types and Relative Amounts of Strain in Cyclic Molecules
- Understanding the Chair Conformations of Cyclohexane Derivatives
- Determining the Relative Stabilities of Conformations of Cyclohexane Derivatives

In Chapter 1 you learned the geometry of the bonds around an atom. For example, the four bonds of an sp^3-hybridized carbon have a tetrahedral geometry. But what happens when several such carbons are bonded together? What is the geometrical relationship between the bonds on different carbons? What is the overall shape of the molecule? Is more than one shape possible? If so, are they different in energy? Can they interconvert? If so, how fast? These and other questions will be answered in this chapter and the next, which discuss the **stereochemistry,** or three-dimensional structures, of organic molecules. In these chapters you will encounter a new type of isomer: stereoisomers. Unlike the constitutional isomers that you have already seen, **stereoisomers** have the same bonds or connectivity, but the bonds are in a different three-dimensional orientation.

This chapter begins with a discussion of a type of stereoisomer that arises because of the presence of a carbon–carbon double bond in a compound. Then a method to distinguish these stereoisomers when naming them is presented. This is followed by a discussion of the various shapes that molecules can assume by rotating about their single bonds.

An understanding of stereoisomers is important because these compounds often have different physical properties and different chemical reactions. There are reactions that occur with only one stereoisomer and not another. There are other reactions that produce only one stereoisomer and not another. This is especially true for biochemical reactions, both in the laboratory and in living organisms. Therefore, an understanding of stereochemistry is essential to the study of organic chemistry.

It is difficult to appreciate the three-dimensional shapes of organic molecules by examination of only the diagrams or pictures of their structures that are shown in

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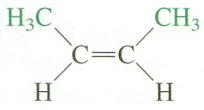
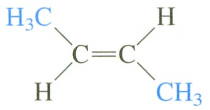
two dimensions on the pages of a book. The use of models is an invaluable aid in understanding the material presented in this chapter. You are strongly encouraged to build models of the molecules discussed in this chapter, at least until you become more comfortable with their three-dimensional structures. Be sure to take advantage of the online computer models for the molecules that are discussed in this chapter.

6.1 Cis–Trans Isomers

Suppose you were asked to draw 2-butene. You would quickly write the structure $CH_3CH{=}CHCH_3$. Now suppose you were asked to carefully show the shape of the molecule, specifically the geometry of the bonds of the carbons involved in the double bond. As discussed in Chapter 3, each carbon of the double bond is sp^2 hybridized and so has a trigonal planar geometry. Furthermore, to have maximum overlap of the *p* orbitals of the pi bond, the two carbons of the double bond and all four atoms attached to them (the two carbons of the methyl groups and the two hydrogens) must lie in the same plane. You would soon discover that there are two ways to draw 2-butene based on these constraints. One has the two methyl groups on the same side of a line that runs through the doubly bonded carbons (on the same side of the double bond), and the other has the two methyl groups on opposite sides of this line (on opposite sides of the double bond):



cis-2-Butene

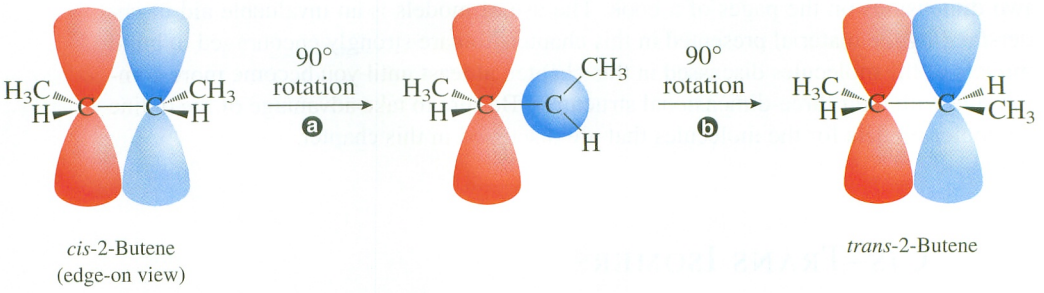


trans-2-Butene

0.33	Dipole moment (Debyes)	0
4°C	Boiling point	1°C
−139°C	Melting point	−106°C

MODEL BUILDING PROBLEM 6.1
Build and compare handheld models of the two possible 2-butenes.

These structures have the same bonds, so they are not constitutional isomers. However, they have a different arrangement of these bonds in three dimensions—they are stereoisomers. Stereoisomers like these, that differ in the placement of groups on one side or the other of the double bond, are called **cis–trans isomers.** The term *cis-* is used to designate the stereoisomer that has like groups on the same side of the double bond and the term *trans-* is used to designate the stereoisomer that has like groups on opposite sides. The *cis-* and *trans*-isomers of 2-butene are different compounds and have different, although similar, physical and chemical properties. For example, although both are nonpolar compounds, *cis*-2-butene has a small dipole moment. The vectors of any small bond dipoles in *trans*-2-butene must cancel because of its shape, so its dipole moment must be zero. The boiling points of the two isomers are quite similar, but the *trans*-isomer melts at a significantly higher temperature because its more linear shape allows it to pack better into a crystal lattice.



The *p* orbitals of the pi bond of *cis*-2-butene are in the plane of the page, and the plane defined by the atoms attached to the carbons of the double bond is perpendicular to the page. To convert to the *trans*-isomer, one of the carbons of the double bond must be rotated about the axis of the double bond.

a Rotation of the right carbon by 90° produces the middle structure. The plane defined by the left CH_3—C—H is now perpendicular to the plane defined by the CH_3—C—H on the right. The red *p* orbital on the left C is in the plane of the page, and the blue *p* orbital on the right C is pointed directly at you, so the two *p* orbitals are also perpendicular to one another. Therefore, there is no stabilizing overlap of these *p* orbitals—the pi bond has been broken.

b An additional rotation of the right carbon by 90° produces *trans*-2-butene.

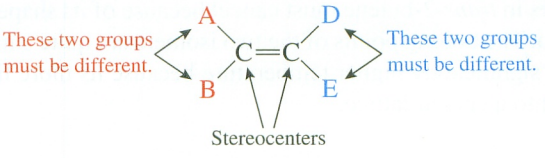
Figure 6.1

INTERCONVERSION OF *CIS*- AND *TRANS*-2-BUTENE BY ROTATION ABOUT THE DOUBLE BOND.

For one cis–trans isomer to convert to the other, rotation about the carbon–carbon double bond must occur as shown in Figure 6.1. As discussed in Chapter 3, such rotation causes the overlap of the *p* orbitals of the pi bond to decrease until, at a rotation of 90°, the *p* orbitals are perpendicular and there is no net overlap. At this point, the pi bond is broken. Continued rotation reverses this process until the pi bond is completely reformed in the other stereoisomer. In Chapter 3 the amount of energy that this process requires was estimated from the difference in the strength of a carbon–carbon double bond and that of a single bond to be approximately 60 kcal/mol (250 kJ/mol). Recall that about 20 kcal/mol (84 kJ/mol) of thermal energy is available at room temperature. Reactions with activation energies less than this amount occur fairly rapidly at room temperature, whereas reactions that require larger amounts of energy are slow. Therefore, interconversion of cis–trans isomers is slow at room temperature (so slow that we say that it does not occur). It is possible to separate cis–trans isomers and study their individual properties.

For an alkene to exhibit cis–trans isomerism, the two groups on one end of the double bond must be different and the two groups on the other end of the double bond must be different. That is, in terms of the following structure, A must be different from B, and D must be different from E. When this is the case, both of the carbons of the double bond are said to be stereocenters. A **stereocenter** or **stereogenic atom** is defined as an atom at which the interchange of two groups produces a stereoisomer.

For cis–trans isomers to exist:



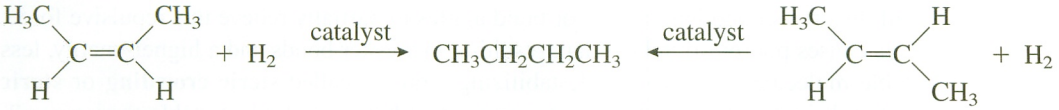
PROBLEM 6.1

Which of these compounds exhibit cis–trans isomerism? Draw both cis–trans isomers when they exist.

a) $CH_3CH_2CH{=}CHCH_3$ **b)** $CH_3CH_2CH{=}CH_2$

c) $CH_3C(CH_3){=}CHCH_3$ **d)** $CH_3C(Cl){=}CHCH_2CH_3$

As illustrated earlier for the 2-butene isomers, cis–trans isomers usually have different physical properties. It should not be surprising, then, that they also often have somewhat different stabilities. The relative stabilities of *cis*-2-butene and *trans*-2-butene can be determined by comparing the heat that is evolved when each of these compounds reacts with hydrogen. (This reaction is called *catalytic hydrogenation* because a catalyst is required.) In the case of the 2-butenes, both of the cis–trans isomers produce the same product, butane, upon catalytic hydrogenation:



When the *cis*-isomer reacts with hydrogen, 28.6 kcal/mol (120 kJ/mol) of heat is produced. When the *trans*-isomer is subjected to the same reaction, 27.6 kcal/mol (115 kJ/mol) of heat is produced. Because the product has the same energy in both reactions, any difference in the heat produced must be due to differences in the energies of the starting alkenes. Because the *cis*-isomer produces more heat, it must be higher in energy (less stable) than the *trans*-isomer. This is best seen by examining a diagram of the energies as shown in Figure 6.2. As can be seen in the diagram, *trans*-2-butene and hydrogen are 27.6 kcal/mol higher in energy than butane, and *cis*-2-butene and hydrogen are 28.6 kcal/mol higher. This means that the *cis*-isomer is 1.0 kcal/mol (4.2 kJ/mol) higher in energy (less stable) than the *trans*-isomer.

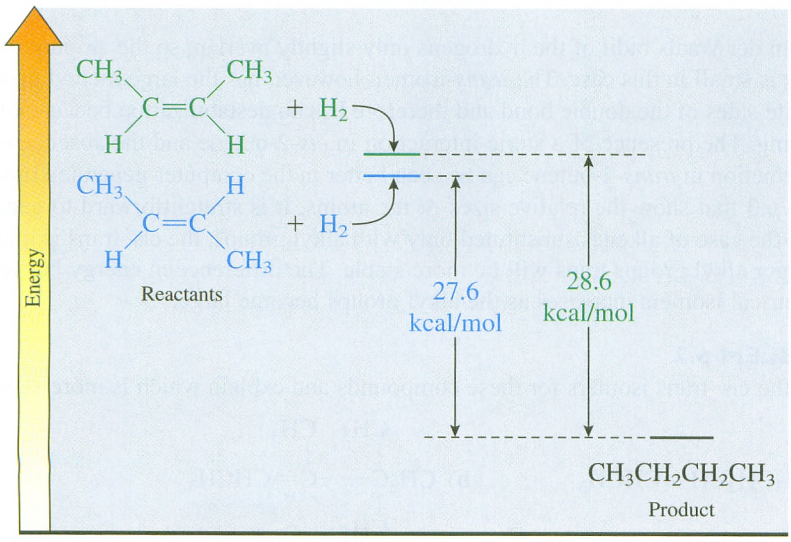


Figure 6.2

ENERGY DIAGRAM FOR THE CATALYTIC HYDROGENATION OF THE ISOMERIC 2-BUTENES.

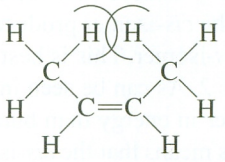
Figure 6.3

COMPUTER-DRAWN MODELS OF *CIS*- AND *TRANS*-2-BUTENE.

cis-2-Butene *trans*-2-Butene

Why is *cis*-2-butene slightly less stable than *trans*-2-butene? Constitutional isomers have different bonds, so it is to be expected that their total bond energies will usually be different. However, in the case of cis–trans isomers the difference must be more subtle than this because the bonds are the same. In this case we must evaluate the increase in energy due to strain in the molecules. **Strain** is any factor that destabilizes a molecule by forcing it to deviate from its optimum bonding geometry.

Different atoms cannot occupy the same region of space. If atoms that are not bonded approach each other too closely (inside their van der Waals radii), they repel each other. A molecule whose structure forces nonbonded atoms too close together will distort its bond lengths and/or bond angles to partially relieve this repulsive force. This causes poorer orbital overlap, resulting in weaker bonds and a higher-energy, less stable molecule. This type of destabilizing strain is called **steric crowding** or **steric strain.** It is this type of strain that causes *cis*-2-butene to be less stable than *trans*-2-butene. In the *cis*-isomer the hydrogens on the methyl groups are forced somewhat too close together because of the rigid geometry of the double bond. This causes a small increase in the energy of the *cis*-isomer due to steric crowding.



The planar geometry of the double bond causes a hydrogen on each of the methyl groups to be forced too close together, resulting in some steric strain.

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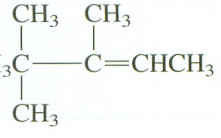
The van der Waals radii of the hydrogens only slightly overlap, so the amount of strain energy is small in this case. The *trans*-isomer, however, has the large methyl groups on opposite sides of the double bond and therefore has no destabilization because of steric crowding. The presence of a steric interaction in *cis*-2-butene and the absence of such an interaction in *trans*-2-butene can be seen better in the computer-generated models in Figure 6.3 that show the relative sizes of the atoms. It is straightforward to generalize that in the case of alkenes substituted only with alkyl groups, the cis–trans isomer with the larger alkyl groups trans will be more stable. The difference in energy between the geometrical isomers increases as the alkyl groups become larger.

PROBLEM 6.2

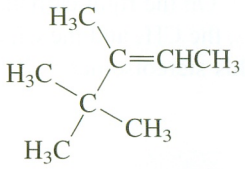
Draw the cis–trans isomers for these compounds and explain which is more stable:

a) $CH_3CH_2CH{=}CHCH_3$

b) 

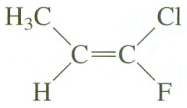
MODEL BUILDING PROBLEM 6.2

Build handheld models of both cis–trans isomers of this compound and compare the amount of steric crowding in each.

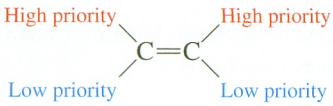


6.2 Designating the Configuration of Cis–Trans Isomers

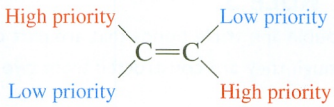
The three-dimensional arrangement of groups about a stereocenter in a molecule is termed its **configuration.** One way to designate the configurations of cis–trans isomers is to use the terms *cis* and *trans*. However, these terms are ambiguous in many instances. For example, is the following isomer of 1-chloro-1-fluoro-1-propene the *cis*- or the *trans*-stereoisomer?



The problem is that *cis* means that the two groups used as references are on the same side of the double bond and *trans* means that they are on opposite sides. But which are the reference groups? Often, two like groups are used as references, as was the case with the 2-butenes. However, the preceding example does not have two like groups. To designate the configuration of such compounds, a set of rules is needed to determine which of the two groups on each end of the double bond has higher priority and will therefore be used as references. To avoid confusion with the older cis–trans method, the newer method uses different terms to indicate whether the high-priority groups are located on the same or opposite sides of the double bond. If the high-priority groups are on the *same side* of the double bond, the configuration is designated ***Z*** (from the first letter of the German word *zusammen,* which means "together"), and if the high-priority groups are on *opposite sides,* the configuration is designated as ***E*** (from the German word *entgegen,* which means "opposite").



Z



E

Priorities are assigned to groups by a series of rules known as the **Cahn-Ingold-Prelog sequence rules,** named after the three chemists who developed them. These rules use the atomic numbers of the atoms attached to the carbons of the double bond.

▶ Rule 1

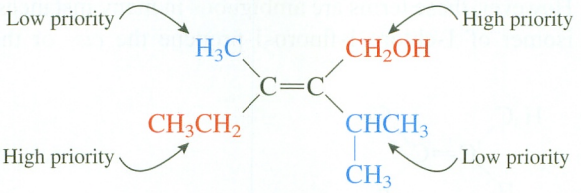
Of the two atoms attached to one carbon of the double bond, the one with the higher atomic number has the higher priority.

This is the only rule needed to assign the configuration of the stereoisomer of chlorofluoropropene shown earlier. Of the two atoms attached to the left carbon of the double bond, C has a higher atomic number than H. Therefore, the methyl group has a higher priority than the hydrogen. On the right carbon, Cl has a higher priority than F. Because the high-priority groups, the CH_3 and the Cl, are on the same side of the double bond, the configuration of this stereoisomer is *Z*. The compound is named (*Z*)-1-chloro-1-fluoro-1-propene.

▶ RULE 2

If the two atoms attached to the carbon are the same, compare the atoms attached to them in order of decreasing priority. The decision is made at the first point of difference.

It may be necessary to continue farther out a chain of atoms until the first point of difference is reached. An application of this rule is shown in the following example:



(*E*)-2-Isopropyl-3-methyl-2-penten-1-ol

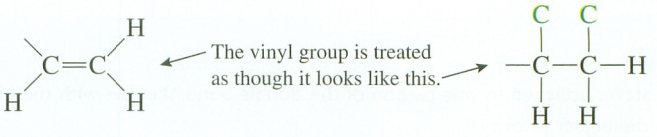
The atoms attached to the carbon on this end of the double bond are both carbons. Therefore, we must compare the three atoms attached to each of these carbons. The atoms bonded to the upper C (the C of the methyl group) are H, H, and H. The atoms bonded to the lower C (the C of the CH_2 of the ethyl group) are C, H, and H. The highest-priority atom on the upper carbon is H, whereas that on the lower carbon is C, so the lower group, the ethyl group, has the higher priority.

The atoms attached to the carbons on this end of the double bond are also both carbons. The upper carbon is bonded to O, H, and H. The lower carbon is bonded to C, C, and H. In order of decreasing priority the first comparison is O versus C. Because O has a higher atomic number, the top group has the higher priority. Note that the decision was made at the first point of difference. The fact that the second group bonded to the lower carbon (a carbon) has a higher atomic number than the second group attached to the upper carbon (a hydrogen) has no bearing on the outcome.

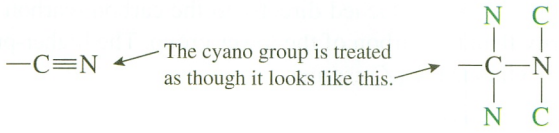
▶ RULE 3

Double and triple bonds that are part of the groups attached to the double bond are treated as though they are constructed from two or three single bonds, respectively.

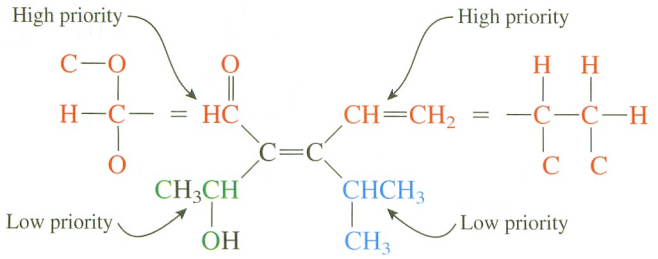
An easy way to visualize this is to replace the second bond of a double bond with an additional single bond to the same kind of atom. This is done for both partners of the double bond, as illustrated here for the vinyl group:



Note that the newly added atoms do not have their valences completed. Similarly, the second and third bonds of a triple bond are replaced with single bonds to the same kind of atom, as shown for the cyano group in the following example:



The following example will help illustrate the use of Rule 3:



On this side of the double bond, the upper (aldehyde) group has higher priority. Its carbon is bonded to O, O, and H, whereas the carbon of the bottom group is bonded to O, C, and H.

On this side of the double bond, the upper (vinyl) group has higher priority. Its carbon is bonded to C, C, and H, but so is the bottom carbon. The next carbon out on the vinyl group is bonded to C, H, and H, whereas the next carbon on the lower group is bonded to H, H, and H.

Because the high-priority groups are on the same side, this is the (*Z*)-isomer.

PROBLEM 6.3

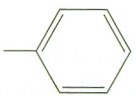
Which of these groups has the higher priority?

a) $-CH_3$ or $-CH_2CH_3$

b) $-\overset{\overset{O}{\|}}{C}OH$ or $-\overset{\overset{O}{\|}}{C}NH_2$

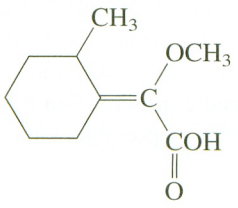
c) $-CH_2CH_2CH_3$ or $-CH_2CH_2CH_2CH_3$

d) $-CH_2CH_2CH_3$ or $-C\equiv N$

e) $-\overset{\overset{CH_3}{|}}{C}HCH_3$ or 

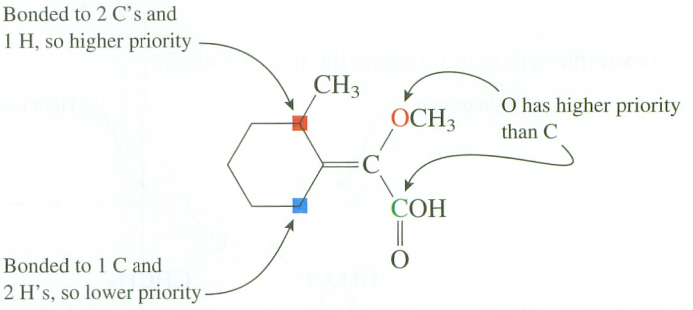
PRACTICE PROBLEM 6.1

Does this alkene have the *Z* or *E* configuration?



Solution

On the left side the upper carbon has higher priority because it is bonded to two C's and one H, whereas the lower carbon is bonded to one C and two H's. On the right side the oxygen of the upper group is attached directly to the carbon–carbon double bond and has a higher priority than the carbon of the lower group. The higher-priority groups are on the same side, so this is the (*Z*)-isomer.



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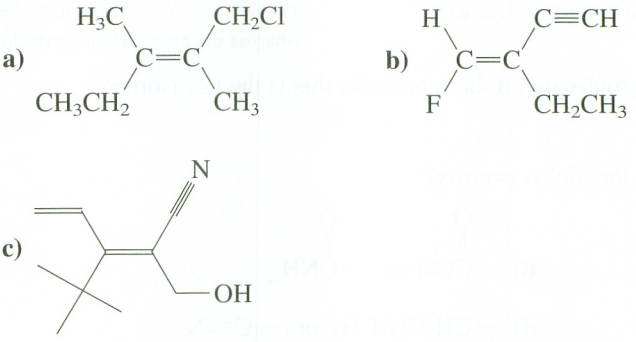
PROBLEM 6.4

Assign these compounds as the *Z* or *E* isomers:

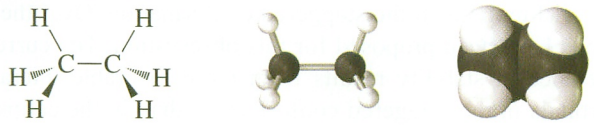


6.3 CONFORMATIONS

Now let's consider the shapes of molecules containing single bonds. As was discussed in Chapter 3, atoms involved in single bonds can rotate about the axis of the bond without affecting the overlap of the orbitals that form that bond. Because the bond energy is not affected, atoms are free to rotate about single bonds. The various shapes that a molecule can assume by rotation about single bonds are called **conformations.** Derek Barton shared the 1969 Nobel Prize in chemistry for his work in the area of conformations.

As a simple example, let's consider the case of ethane. Rotation about the carbon–carbon sigma bond results in a number of different conformations for this molecule. There are two extremes for these conformations, as shown in Figure 6.4. The **eclipsed conformation** has each hydrogen on one carbon as close as possible to one hydrogen on the other carbon. The **staggered conformation** has the hydrogens on one carbon as far from the hydrogens on the other as possible. Other conformations are intermediate between these two extremes.

ⓐ Eclipsed Conformation

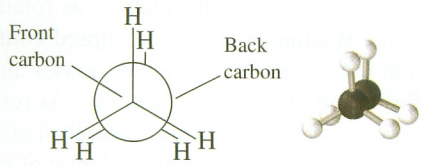


Ethane

Each carbon–hydrogen bond on one carbon of the eclipsed conformation of ethane is directly in line with a carbon–hydrogen bond on the other carbon. This is easier to see if we view the molecule end-on—that is, down the carbon–carbon bond. A drawing of such a view, called a Newman projection, is as follows:

Newman projection

Important Convention



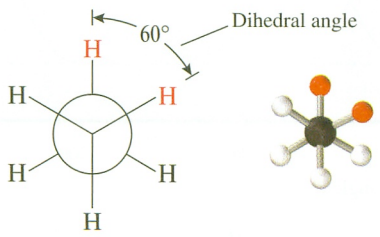
In a Newman projection the molecule is viewed end-on so that one carbon is directly behind the other. By convention, the front carbon is represented by the intersection of its three carbon–hydrogen bonds and the back carbon is represented by a circle. Here it is easy to see that the back carbon–hydrogen bonds lie directly behind the front carbon–hydrogen bonds. The front hydrogens eclipse the back hydrogens.

ⓑ Staggered Conformation

Ethane

In the staggered conformation of ethane the carbon–hydrogen bond on one carbon bisects the angle between two of the carbon–hydrogen bonds on the other carbon. Again, this can better be seen in the Newman projection:

Newman projection



Note how each carbon–hydrogen bond bisects the angle between two carbon–hydrogen bonds on the other carbon. Each hydrogen on the front carbon is perfectly staggered between two hydrogens on the back carbon. The hydrogens on the back carbon are similarly staggered. The **dihedral angle** is defined as the angle between a marker group on the front carbon and one on the back carbon in this flat projection. In this case, if the red hydrogens are the markers, the dihedral angle is 60°.

Figure 6.4

ⓐ ECLIPSED AND ⓑ STAGGERED CONFORMATIONS OF ETHANE AND THEIR NEWMAN PROJECTIONS.

Experiments have shown that the eclipsed conformation is slightly less stable (by 2.9 kcal/mol [12.1 kJ/mol]) than the staggered conformation. Over the years, a variety of explanations have been proposed for this observation. The current hypothesis is that this difference in stability results from more favorable interactions among the molecular orbitals in the staggered conformation than in the eclipsed conformation. We need not be concerned with the details of this explanation at this point. The important fact is that the staggered conformation is more stable than the eclipsed conformation. The destabilization caused by eclipsed bonds is called **torsional strain.** Because there are three eclipsed pairs of carbon–hydrogen bonds and the total energy increase caused by these interactions is 2.9 kcal/mol (12.1 kJ/mol), each of these eclipsing interactions destabilizes the eclipsed conformation by about 1 kcal/mol (4 kJ/mol).

Now consider what happens to the energy of the conformations as rotation occurs about the carbon–carbon bond of ethane. Beginning with the eclipsed conformation, the energy is at its highest point. As rotation occurs, the energy decreases until a minimum is reached at the staggered conformation after a rotation of 60°. As rotation continues, the energy increases until a new eclipsed conformation is reached at 120°. This process is repeated twice more as rotation proceeds through 360°. A plot of energy versus dihedral angle for this rotation is shown in Figure 6.5. The staggered conformations are located at minima on this plot, separated by 2.9 kcal/mol (12.1 kJ/mol) energy hills at the eclipsed conformations. Because 20 kcal/mol (83.7 kJ/mol) of thermal energy is available at room temperature, there is plenty of energy to allow an ethane molecule in

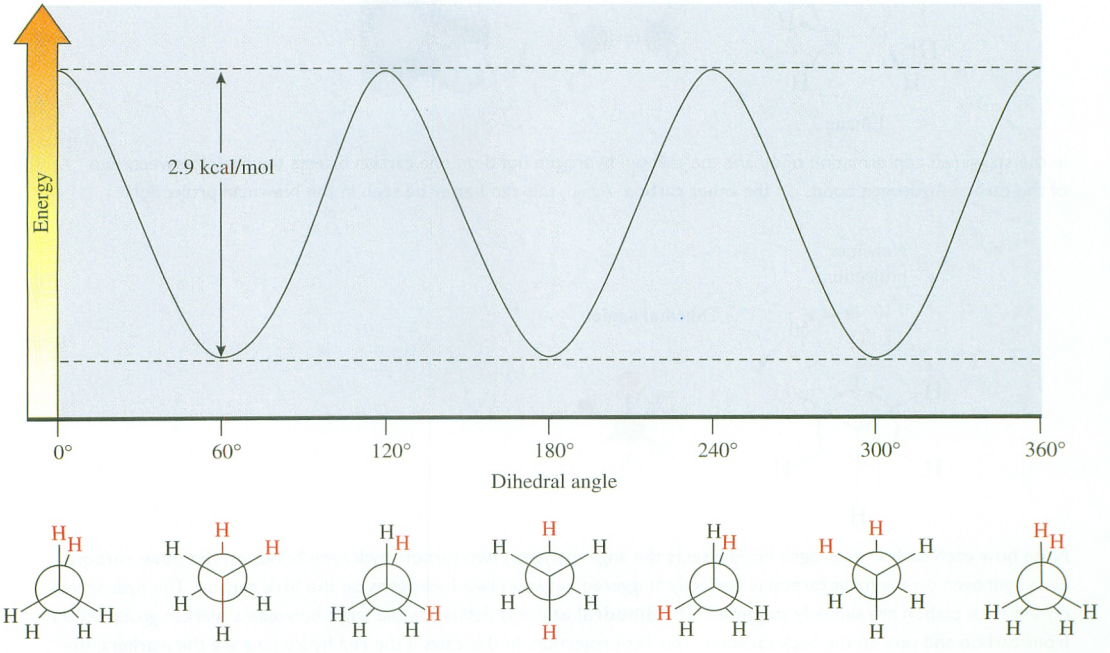
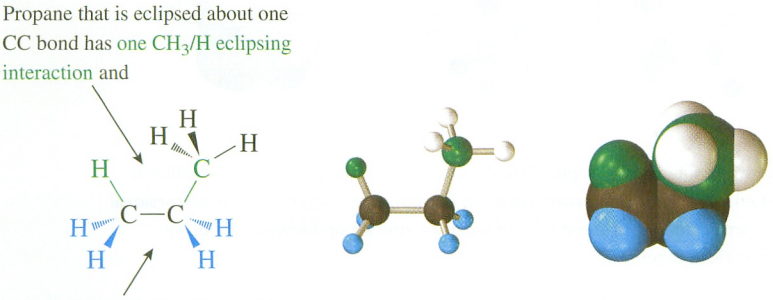


Figure 6.5

PLOT OF ENERGY VERSUS DIHEDRAL ANGLE FOR CONFORMATIONS OF ETHANE.

a staggered conformation to climb over the energy barrier posed by the eclipsed conformation and rotate to another staggered conformation. This rotation occurs very rapidly at room temperature. The barriers for rotations about most single bonds are in the 3 to 5 kcal/mol (12–21 kJ/mol) range, so rotations about most single bonds are fast at room temperature. Therefore, different conformations cannot be separated or isolated and are not usually considered to be isomers. We say that there is *free rotation* about single bonds.

Next, let's consider the case of propane. Conformational analysis can be done about either of the two identical carbon–carbon bonds. Again there are two limiting conformations: staggered and eclipsed. The only difference between this example and the analysis of ethane done previously is that here there are two hydrogen–hydrogen eclipsing interactions and one hydrogen–methyl eclipsing interaction.



Propane

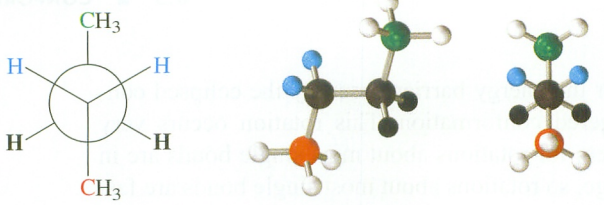
It is to be expected that the repulsion between the eclipsed methyl and hydrogen is slightly larger than that between two hydrogens. In fact, the eclipsed conformation of propane is 3.3 kcal/mol (13.8 kJ/mol) higher in energy than the staggered conformation. If each of the H with H interactions contributes about 1 kcal/mol (4 kJ/mol) to this value, as was the case for ethane, then the eclipsing interaction between the methyl and the hydrogen must contribute about 1.3 kcal/mol (5.4 kJ/mol) in repulsion energy. This is due primarily to torsional strain between the C—H bond and the C—C bond, along with a smaller contribution due to steric strain between the hydrogen on the carbon and the hydrogens on the methyl group. The energy versus dihedral angle plot for propane looks just like the one for ethane except that the energy difference between the staggered and eclipsed conformations is 3.3 kcal/mol.

PROBLEM 6.5

Draw a plot of energy versus dihedral angle for the conformations of propane about one of the C—C bonds.

Butane provides a more complex example. Here there are two different types of carbon–carbon bonds. Analysis of the conformations available by rotation about the bond between carbon 1 and carbon 2 (or carbon 3 and carbon 4) is very similar to the analysis of propane, with the difference that there is an ethyl group on one carbon rather

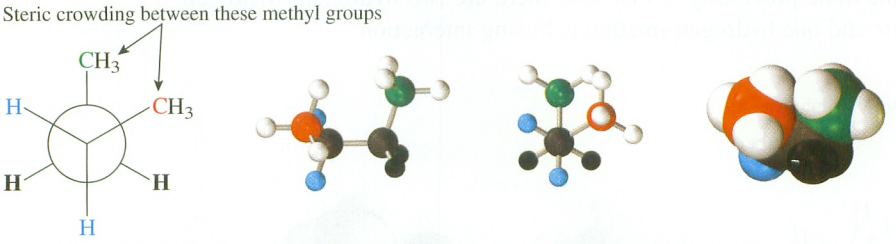
(a) Anti Conformation



Butane

Two groups, the methyl groups in this case, are said to be anti if the dihedral angle between them is 180°. The anti conformation is the most stable conformation of butane because it is staggered and has the two large methyl groups as far apart as possible.

(b) Gauche Conformation

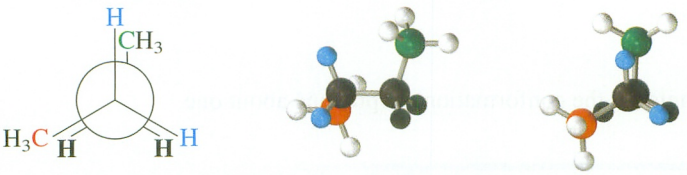


Two groups are said to be gauche when the dihedral angle between them is 60°. The gauche conformation is 0.8 kcal/mol (3.3 kJ/mol) higher in energy than the anti conformation. Because it is staggered, it has no torsional strain. Its higher energy is due to a small amount of steric strain caused by interaction between the bulky methyl groups, which are a little too close together.

(c) Eclipsed Conformation

This eclipsed conformation has two H with H eclipsing interactions and one CH_3 with CH_3 eclipsing interaction. The eclipsing interaction between the methyl groups is more destabilizing than that between the hydrogens. This conformation is about 4.5 kcal/mol (19 kJ/mol) less stable than the anti conformation. If the two H with H interactions contribute 1 kcal/mol each to this value, as was the case for ethane, then the CH_3 with CH_3 interaction must contribute the remaining 2.5 kcal/mol (10.5 kJ/mol). This value is due to both torsional and steric strain.

(d) Eclipsed Conformation



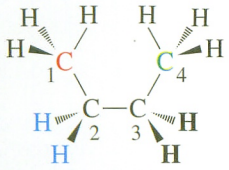
This eclipsed conformation has two CH_3 with H interactions and one H with H interaction. If a CH_3 with H interaction here costs the same amount of energy as it did in the case of propane (1.3 kcal/mol), then this conformation would be expected to be destabilized by 2(1.3) + 1 = 3.6 kcal/mol (15 kJ/mol). This value is in reasonable agreement with the experimental value of 3.7 kcal/mol (15.5 kJ/mol).

Active Figure 6.6

ORGANIC Chemistry Now™

CONFORMATIONS OF BUTANE. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

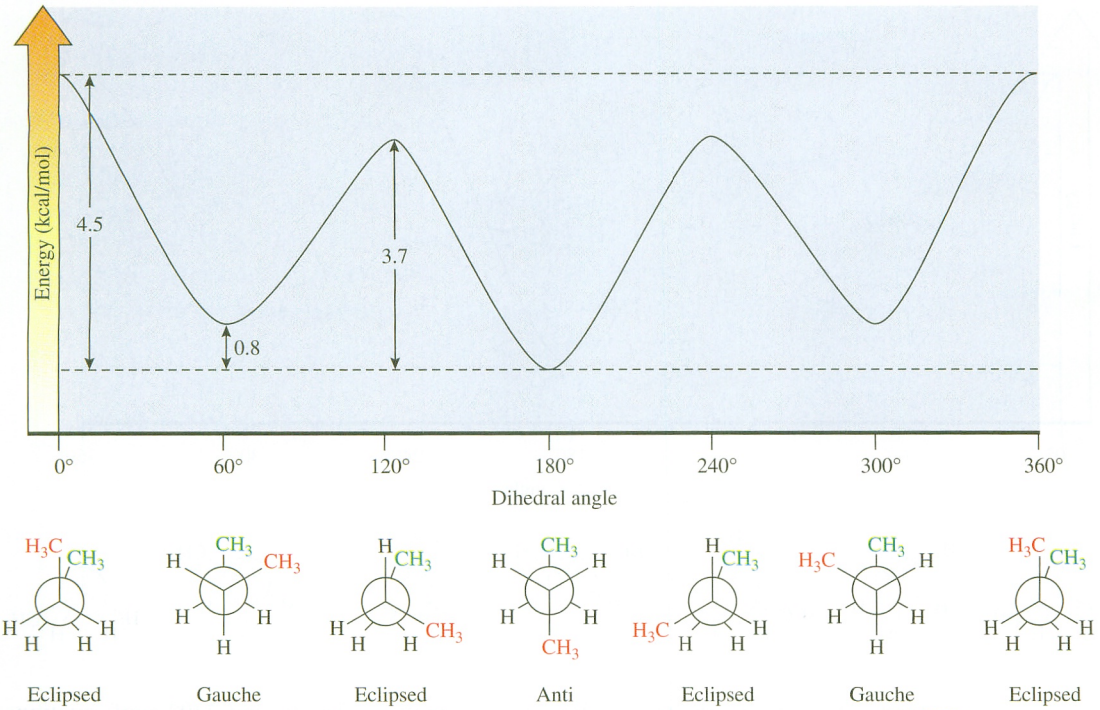
than a methyl group. However, conformational analysis about the bond between carbon 2 and carbon 3 provides a more interesting situation. In this case, each carbon has one methyl group and two hydrogens. The various conformations lead to a number of different interactions, shown in Figure 6.6.



Butane

Conformational analysis about the C-2—C-3 bond of butane is more complex than previous examples because each carbon has a methyl and two hydrogens bonded to it. Several different interactions occur in the conformations.

A plot of the energies of these conformations, with the methyl groups used as the markers for the dihedral angles, is shown in Figure 6.7. The lowest-energy minimum on this plot is located at the anti conformation. There are also minima at the two gauche conformations that are 0.8 kcal/mol (3.3 kJ/mol) less stable than the anti conformation. The highest-energy barrier on the plot, at the conformation where the methyl groups are eclipsed, is 4.5 kcal/mol (19 kJ/mol) higher in energy than the anti conformation. Therefore, rotation about this carbon–carbon bond is fast at room temperature. The gauche and anti conformations are in equilibrium, about 70% of the molecules having the more stable anti conformation at any given instant.

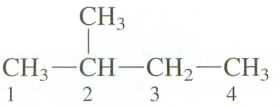


Active Figure 6.7 ORGANIC Chemistry Now™

PLOT OF ENERGY VERSUS DIHEDRAL ANGLE FOR CONFORMATIONS OF BUTANE. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

PRACTICE PROBLEM 6.2

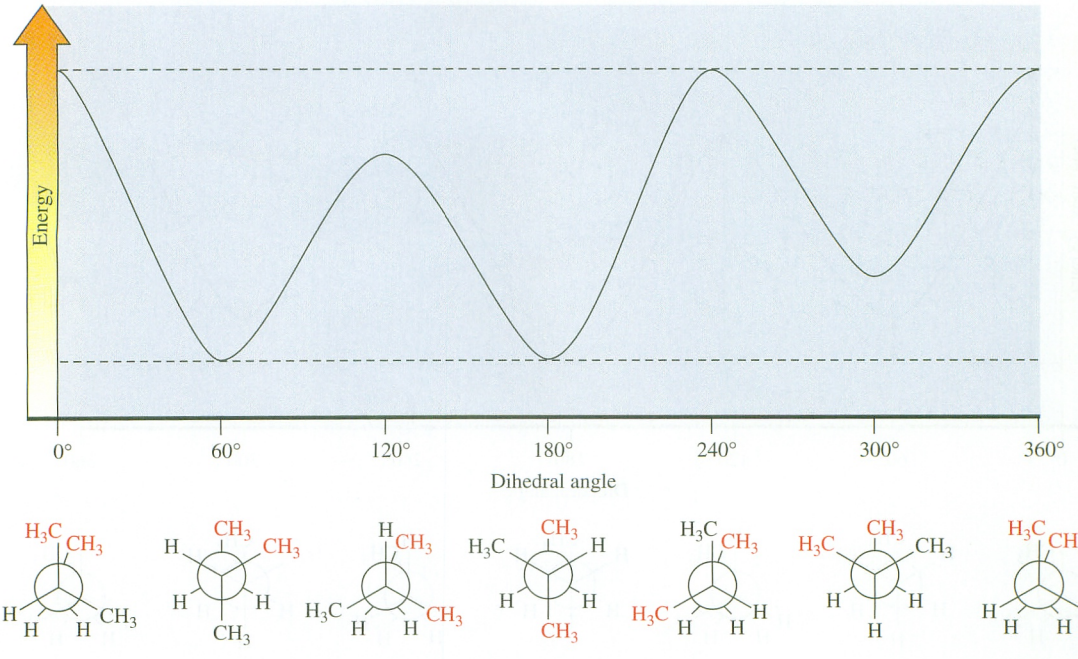
Draw a plot of energy versus dihedral angle for the conformations of 2-methylbutane about the C2—C3 bond.



Strategy

Start by drawing the conformations about the C2—C3 bond using Newman projections. Begin with an eclipsed conformation and rotate the front (or back) carbon by 60°. Continue to rotate the carbon in the same direction, drawing the conformation after each 60° rotation until the original conformation is reached after a total rotation of 360°. Now assign the energies of the conformations. In general, eclipsed conformations are higher in energy than staggered conformations, and conformations that have larger groups eclipsed are higher in energy than those that have smaller groups eclipsed. Next evaluate the energies of the staggered conformations; the energy of the conformation increases as the number of gauche interactions increases. Be careful to place conformations with the same interactions at the same energy.

Solution



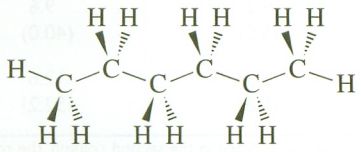
First, let's examine the three eclipsed conformations. The 0° and 240° conformations both have one CH_3 with CH_3, one CH_3 with H, and one H with H eclipsing interaction,

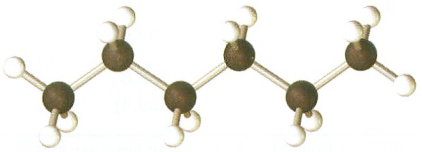
so they have the same amount of strain energy. The 120° conformation has three CH_3 with H eclipsing interactions, so it has less strain energy than the others—it is at lower energy. The 60° and 180° staggered conformations have one gauche interaction and therefore are lower in energy than the 300° staggered conformation, which has two gauche interactions.

PROBLEM 6.6

Draw a Newman projection of the highest-energy conformation of 2,3-dimethylbutane about the C2—C3 bond.

Analysis of the conformations of other alkanes can be done in a similar manner. For any linear alkane the most stable conformation is the so-called zigzag conformation, which is anti about all of the carbon–carbon bonds. The zigzag conformation for hexane follows:





Hexane

Free rotation about the carbon–carbon bonds generates a large number of other conformations that are gauche about one or more of these bonds. Although the zigzag conformation is the most stable one, many of the others are only slightly higher in energy and are readily attainable at room temperature. The shape of an individual molecule changes rapidly, twisting and turning among these various possibilities. Finally, the presence of polar substituents can dramatically affect and complicate conformational preferences because of interactions among their dipoles and hydrogen bonding. Factors such as these help control not only the shape but also the function of complex biological molecules, such as enzymes and other proteins.

6.4 Conformations of Cyclic Molecules

Because their carbon chains are confined in rings, cycloalkanes are much less flexible than noncyclic (or acyclic) alkanes. The number of conformations available is dramatically reduced. Furthermore, cycloalkanes are often held in shapes that cause them to have considerable strain energy. One way to measure this strain energy in the laboratory is to burn the alkane in a calorimeter and measure the amount of heat that is produced (the heat of combustion). The heat of combustion must first be corrected for the number of carbons and hydrogens in the ring. For example, cyclohexane (C_6H_{12}) has twice as many atoms as cyclopropane (C_3H_6) and would be expected to produce twice as much heat on a per mole basis, other factors being equal. The easiest way to correct for this is to divide the heat of combustion per mole by the number of CH_2 groups in the ring. This gives a heat of combustion "per mole of CH_2 group." This value can then be

Table 6.1 Heats of Combustion and Strain Energies of Some Cycloalkanes

Ring Size	Heat of Combustion per CH_2	Strain Energy per CH_2	Total Ring Strain
3	166.3 (695.8)	8.9 (37.2)	26.7 (111.6)
4	163.9 (685.8)	6.5 (27.2)	26.0 (108.8)
5	158.7 (664.0)	1.3 (5.4)	6.5 (27.0)
6	157.4 (658.6)	0	0
7	158.3 (662.3)	0.9 (3.7)	6.3 (25.9)
8	158.6 (663.6)	1.2 (5.0)	9.6 (40.0)
9	158.8 (664.4)	1.4 (5.8)	12.6 (52.2)

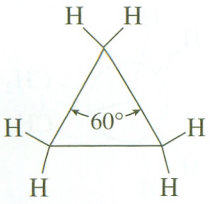
Units are kcal/mol. Units for values in parentheses are kJ/mol. To obtain the values listed in the second column, the total heats of combustion were divided by the number of carbons in the ring. Values in the third column were obtained by subtracting 157.4 (the heat of combustion per CH_2 for cyclohexane) from the values in the second column. Values in the fourth column were calculated by multiplying values in the third column by the number of carbons in the ring.

compared to that of a standard compound that has no strain, such as an unbranched, long-chain alkane.

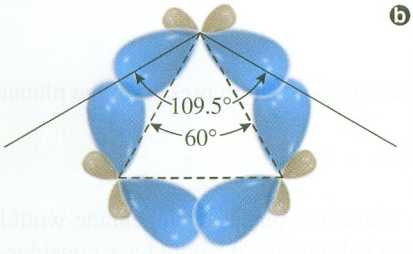
Such heat of combustion values for the cycloalkanes ranging in size from 3 to 9 carbons are provided in Table 6.1. The lowest heat of combustion per CH_2 group is found for cyclohexane, which is usually considered to be free of strain. The extra heat produced by the other cycloalkanes can then be attributed to their strain energies. For example, the heat of combustion per CH_2 for cyclopropane is 166.3 kcal/mol (696 kJ/mol), and that for cyclohexane is 157.4 kcal/mol (659 kJ/mol). The difference, 8.9 kcal/mol (37 kJ/mol), is the amount of strain energy per CH_2 group for cyclopropane. The total strain energy for cyclopropane is three times this value, 26.7 kcal/mol (111 kJ/mol), because cyclopropane has three CH_2 groups. Values for the strain energy per CH_2 group and total ring strain for the other cycloalkanes are also provided in Table 6.1. Note that cyclopropane and cyclobutane have large amounts of strain compared to cyclohexane, whereas the other cycloalkanes have much smaller amounts.

By examining the conformations of the cycloalkanes, we are able to determine the origin of these strain energies. Let's begin with the smallest one, cyclopropane, and see what causes the large amount of strain energy that it has (Figure 6.8).

From heat of combustion data, cyclopropane has 26.7 kcal/mol (111.6 kJ/mol) of strain energy. Most of this strain is due to angle strain, but the contribution due to torsional strain is also significant. As we will see later, this strain energy causes cyclopropane to be more reactive than a normal alkane or cycloalkane. However, even though cyclopropane rings are reactive, they are fairly common in organic chemistry.

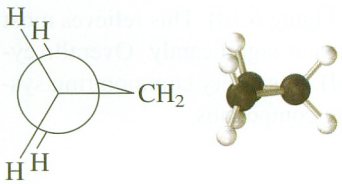


a The three carbons of cyclopropane form an equilateral triangle. The C—C—C angle is 60°. However, if the hybridization at each carbon is sp^3, as would be expected from the structure, then the angles between the sp^3 hybrid AOs are 109.5°.



The orbitals forming the C—C bonds of cyclopropane

b Because the angle between the sp^3 hybrid AOs on one carbon is wider than the angle between the carbons to which these orbitals are bonding, the orbitals cannot point directly toward the carbons. Instead, as shown here, they point slightly outside of a line connecting the nuclei. Because the orbitals of a bond do not point directly at each other, the amount of overlap is decreased. This causes the C—C bonds of cyclopropane to be weaker than normal C—C bonds. This type of destabilization is called **angle strain.**



c In addition to angle strain, cyclopropane has a significant amount of torsional strain. This can best be seen by looking at a Newman projection down any of the C—C bonds. As can be seen in this diagram, each C—C bond is held in an eclipsed conformation by the rigidity of the molecule.

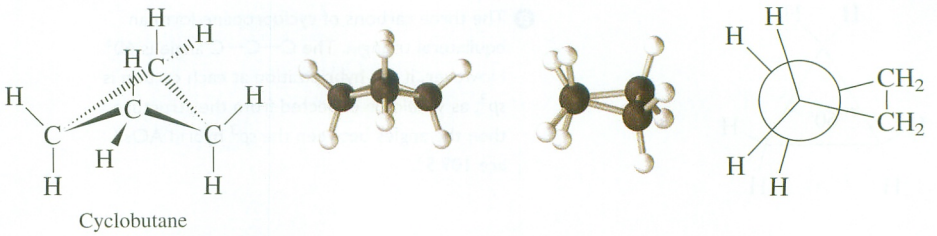
Figure 6.8

CYCLOPROPANE. a BOND ANGLES, b ANGLE STRAIN, AND c TORSIONAL STRAIN.

MODEL BUILDING PROBLEM 6.3

Build a model of cyclopropane and examine its strain.

If the four carbons of cyclobutane lie in a plane, then its carbons form a square. The angles of a square are 90°, so it is expected that cyclobutane also has some angle strain, although not as much as cyclopropane. Planar cyclobutane would also be eclipsed about each C—C bond and would have considerable torsional strain. As the carbons of cyclobutane are distorted from planarity, torsional strain decreases while angle strain increases. For small distortions the increase in angle strain is less than the decrease in torsional strain. Therefore, the lowest-energy conformation of cyclobutane is slightly nonplanar, with an angle between the planes of the carbons of about 35° (Figure 6.9). Cyclobutane has some angle strain and some torsional strain contributing to its total strain energy of 26.0 kcal/mol (108.8 kJ/mol). A Newman projection shows how twisting the carbons out of planarity results in less torsional strain. The hydrogens are no longer exactly eclipsed. Although cyclobutane has less strain than cyclopropane, cyclobutane rings are less common than cyclopropane rings because, as we shall see later, they are more difficult to prepare.



Cyclobutane

Figure 6.9
CYCLOBUTANE.

MODEL BUILDING PROBLEM 6.4

Build a model of cyclobutane. Examine the various types of strain present in the planar and nonplanar geometries.

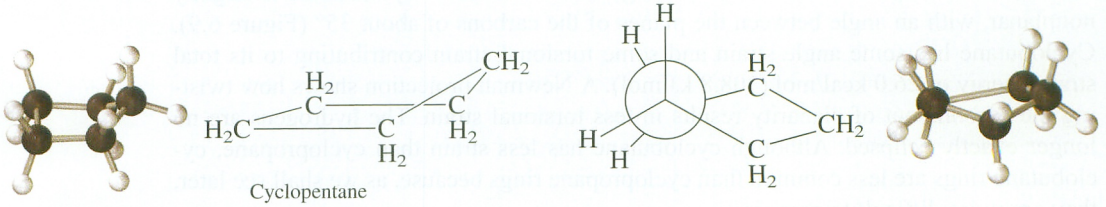
The angles of a regular pentagon are 108°. Therefore, planar cyclopentane would have little or no angle strain. However, like planar cyclobutane, it would have considerable torsional strain because each C—C bond would be held in an eclipsed conformation. It is to be expected, then, that cyclopentane will distort from planarity to relieve this torsional strain. In one low-energy conformation, one carbon folds out of the plane so that the overall shape is somewhat like an envelope (Figure 6.10). This relieves most of the torsional strain without increasing the angle strain significantly. Overall, cyclopentane has very little strain, 6.5 kcal/mol (27 kJ/mol). It is a very common ring system and is widely distributed among naturally occurring compounds.

MODEL BUILDING PROBLEM 6.5

Build a model of cyclopentane. Examine the various types of strain present in the planar and nonplanar geometries.

6.5 CONFORMATIONS OF CYCLOHEXANE

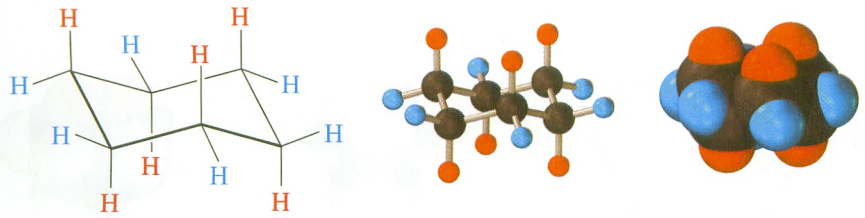
The cyclohexane ring is very important because it is virtually strain free. This is one of the reasons why compounds containing six-membered rings are very common. If cyclohexane were planar, its C—C—C angles would be 120°—too large for the 109.5° angle of sp^3 hybrid AOs. However, the angles of the ring decrease as it becomes nonplanar. There are two nonplanar conformations, called the **chair conformation** and the **boat conformation,** that are completely free of angle strain. These conformations are shown in Figures 6.11 and 6.12, respectively. The chair conformer of cyclohexane is



Cyclopentane

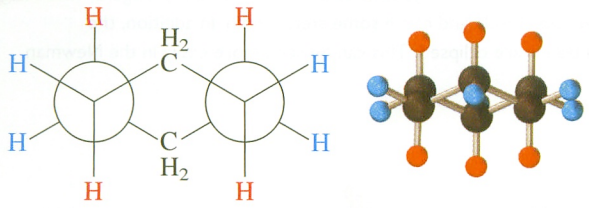
Figure 6.10
CYCLOPENTANE.

ⓐ Chair Conformation



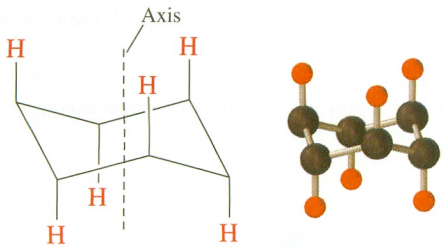
All of the C—C—C bond angles are 109.5°, so this comformation has no angle strain. In addition, it has no torsional strain because all of the C—H bonds are perfectly staggered. This can best be seen by examining a Newman projection down C—C bonds on opposite sides of the ring:

ⓑ Newman Projection



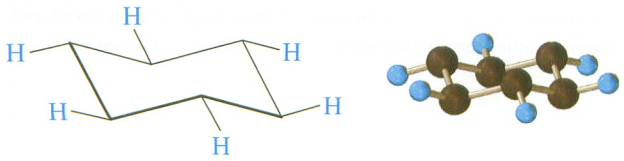
The staggered arrangement of all the bonds can be seen clearly in the Newman projection. This same picture is seen when the projection is viewed down any C—C bond. All the C—C bonds in the molecule are in conformations in which the hydrogens are perfectly staggered.

ⓒ Axial Hydrogens



In the chair conformation cyclohexane has two different types of hydrogens. The bonds to one type are parallel to the axis of the ring. These are called axial hydrogens. The axial bonds alternate up and down around the ring.

ⓓ Equatorial Hydrogens



The other hydrogens are directed outward from the ring. They are called equatorial hydrogens because they lie around the "equator" of the ring. Now go back to structure ⓐ, in which both types of hydrogens are shown, and identify the axial hydrogens (red) and the equatorial hydrogens (blue). Also examine the view of the axial and equatorial hydrogens provided by the Newman projection.

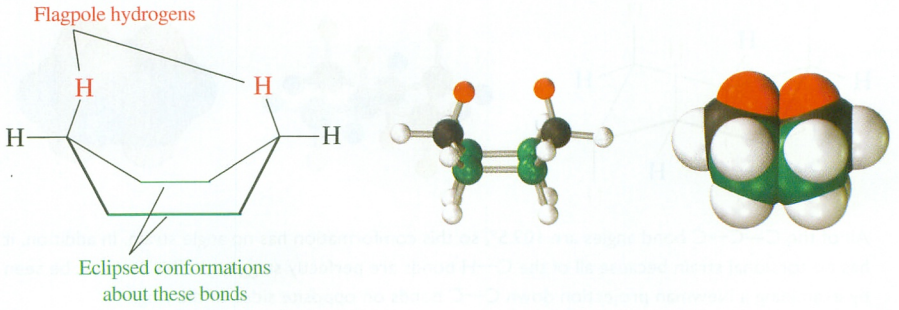
Figure 6.11

THE CHAIR CONFORMATION OF CYCLOHEXANE.
ⓐ CHAIR CONFORMATION,
ⓑ NEWMAN PROJECTION,
ⓒ AXIAL HYDROGENS, AND
ⓓ EQUATORIAL HYDROGENS.

Figure 6.12

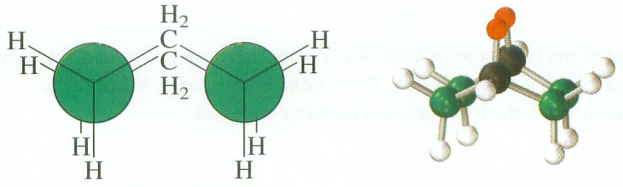
THE BOAT CONFORMATION OF CYCLOHEXANE. (a) BOAT CONFORMATION, (b) NEWMAN PROJECTION, AND (c) TWIST BOAT CONFORMATION.

(a) Boat conformation



Like the chair conformation, all of the C—C—C bond angles of the boat conformation are 109.5°, so it has no angle strain. However, it does have other types of strain. The two red hydrogens, called flagpole hydrogens, approach each other too closely and cause some steric strain. In addition, the conformations about the green bonds are eclipsed. This can be seen more easily in the Newman projection down these bonds:

(b) Newman Projection

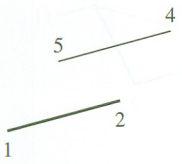


The Newman projection shows that two bonds of the boat conformation are eclipsed. The torsional strain due to these eclipsing interactions and the steric strain due to the interaction of the flagpole hydrogens make the boat conformation higher in energy than the chair conformation. The boat conformation is flexible enough to twist somewhat to slightly decrease its overall strain energy.

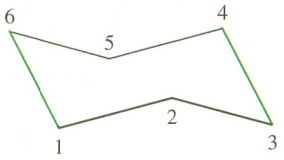
(c) Twist Boat Conformation

In the twist boat conformation the "bow" and the "stern" of the boat have been twisted slightly. Although this decreases the flagpole interaction and relieves some of the torsional strain, angle strain is introduced. Overall, the twist boat conformation is a little more stable than the boat conformation but not nearly as stable as the chair conformation.

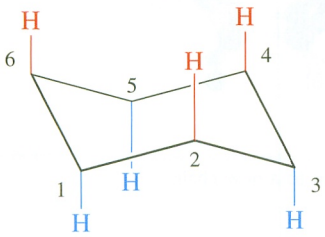
perfectly staggered about all of the C—C bonds and therefore has no torsional strain either—it is strain free. The boat conformer, on the other hand, has both steric strain, due to interactions of the flagpole hydrogens, and torsional strain. It is about 6 kcal/mol (25 kJ/mol) less stable than the chair conformer. Some of the steric and torsional strain



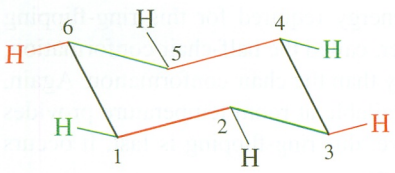
❶ To draw a good cyclohexane chair conformation, first draw two parallel lines, sloping upward and slightly offset. These are the C—C bonds between carbons 1 and 2 and carbons 4 and 5.



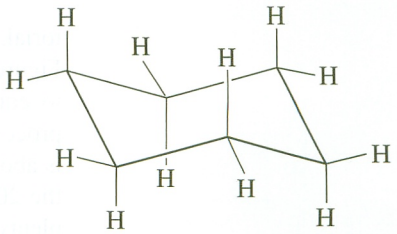
❷ Add carbon 6 to the left and above these lines and carbon 3 to the right and slightly below and draw the C—C bonds. Note how bonds on opposite sides of the ring are drawn parallel (the C-1—C-6 bond is parallel to the C-3—C-4 bond, and so on).



❸ Add the axial C—H bonds. These are drawn up from carbons 2, 4, and 6 and down from carbons 1, 3, and 5.



❹ The equatorial C—H bonds should point outward from the ring. They are drawn parallel to the C—C bond once removed, that is, the equatorial C—H bond on C-1 is drawn parallel to the C-2—C-3 (or C-5—C-6) bond, and the C—H bond on C-3 is drawn parallel to the C-1—C-2 (or C-4—C-5) bond, and so on.



❺ The completed structure should look like this.

Figure 6.13

FIVE STEPS FOR DRAWING CHAIR CYCLOHEXANE.

of the boat can be relieved by twisting. The twist boat conformation is about 5 kcal/mol (21 kJ/mol) less stable than the chair conformation.

Figure 6.11 also shows that there are two different types of hydrogens, called **axial** hydrogens and **equatorial** hydrogens, in the chair conformer of cyclohexane. The axial C—H bonds are parallel to the axis of the ring; the equatorial C—H bonds project outward from the ring around its "equator." Steps to help you learn to draw the chair conformation of cyclohexane, including the axial and equatorial hydrogens, are provided in Figure 6.13.

The chair conformation of cyclohexane is not rigid. It can convert to a twist boat conformation and then to a new chair conformation in a process termed ring-flipping, as shown Figure 6.14 (not all the hydrogens are shown for clarity).

In the ring-flipping process, C-1 flips up to give a twist boat. Then C-4 can flip down to produce another chair conformation. When opposite carbons flip like this, all axial and equatorial bonds interconvert; that is, all hydrogens that were axial are converted to equa-

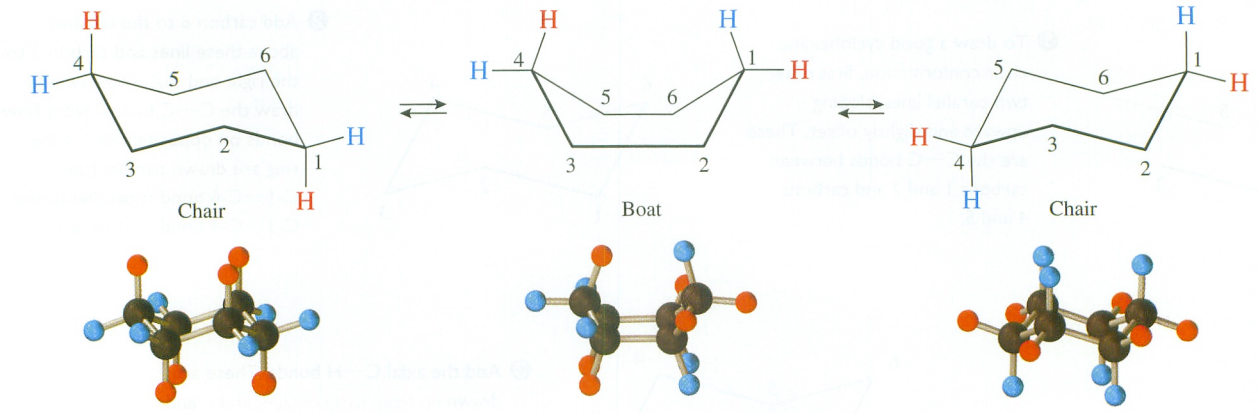


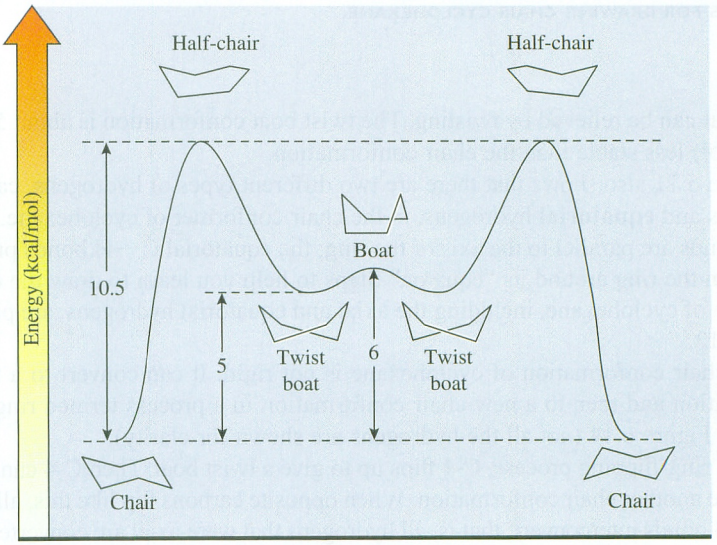
Figure 6.14

RING-FLIPPING. Chair cyclohexane converts to a boat and then to a new chair.

torial, and all hydrogens that were equatorial are converted to axial. This can be seen in Figure 6.14, in which the red hydrogens, which are axial in the left chair, are converted to equatorial hydrogens in the right chair. The energy required for this ring-flipping process is shown in Figure 6.15. The highest barrier, called the half-chair conformation, is about 10.5 kcal/mol (44 kJ/mol) higher in energy than the chair conformation. Again, the 20 kcal/mol (83.7 kJ/mol) of energy that is available at room temperature provides plenty of energy to surmount this barrier; therefore, this ring-flipping is fast. It occurs about 100,000 times per second at room temperature.

Figure 6.15

ENERGY DIAGRAM FOR THE CYCLOHEXANE RING-FLIPPING PROCESS.



MODEL BUILDING PROBLEM 6.6

Build a model of cyclohexane.

a) Examine the strain present when the geometry is planar.
b) Examine the strain present in the boat conformation.
c) What strain is introduced in the twist boat conformation? What strain is relieved?
d) Examine the strain present in the chair conformation. Examine the conformations about one of the CC bonds. Identify the axial and equatorial hydrogens.
e) Try a ring flip with your model. Label an axial hydrogen and determine what happens to it when the ring flips.

MODEL BUILDING PROBLEM 6.7

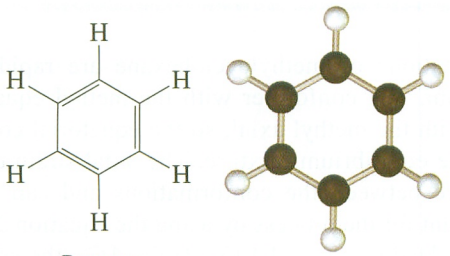
Draw a chair cyclohexane. Show the axial and equatorial hydrogens.

6.6 CONFORMATIONS OF OTHER RINGS

Conformational analysis of rings larger than cyclohexane is more complicated. These rings are also less common than cyclohexane, so we discuss their conformations only briefly. As can be seen from Table 6.1, the seven-membered ring compound cycloheptane has only a small amount of strain. Obviously, it is nonplanar to avoid angle strain. It does have some torsional strain, but the overall strain is comparable to that of cyclopentane. It is a fairly common ring system.

Larger rings, having from 8 to 11 carbons, have somewhat more strain than cycloheptane. They are nonplanar, but even so, they seem to have some strain due to bond angles that are too large for the tetrahedral bond angle of 109.5°. They also have some torsional strain. In addition, these rings have a new type of strain, called **transannular** or **cross-ring strain.** This occurs because some C—H bonds are forced to point toward the center of the ring. The hydrogens of these bonds experience steric crowding from their interactions with atoms on the other side of the ring. Rings of 12 or more carbons no longer have transannular strain and are essentially strain-free.

Compounds that contain a benzene ring are also quite common and important. The carbons of benzene are sp^2 hybridized, with bond angles of 120°, which match exactly the angles of a regular hexagon. Thus, benzene is a planar molecule with no angle strain. It is rigid because any deviation from planarity would increase angle strain and decrease the overlap of the *p* orbitals of the conjugated pi system.



Benzene

In summary, small (3- and 4-membered) rings have a large amount of strain, due primarily to angle strain with some contribution from torsional strain. Rings that have

5, 6, and 7 members have very little strain. Rings that have 8, 9, 10, and 11 members have somewhat more strain, due to a variety of interactions. Large rings (12-membered and larger) have very little strain. However, it is not just the stability of a ring that determines whether it is commonly found but also the probability of its formation. The rings that are most commonly encountered in organic compounds are those that have 3, 5, 6, and 7 members. A discussion of the reasons for this is presented in Section 8.13.

6.7 Conformations of Cyclohexanes with One Substituent

What happens when there is a substituent on the cyclohexane ring? Let's consider methylcyclohexane as a simple example. As before, there are two chair conformations, which interconvert by the ring-flipping process. In this case, however, the two conformations are not identical. As shown in Figure 6.16, the methyl group is equatorial in one conformation and axial in the other. The conformation with the axial methyl is less stable than the conformation with the equatorial methyl by 1.7 kcal/mol (7.1 kJ/mol) because of steric interactions between the methyl and the axial hydrogens on C-3 and C-5. (These are often called **1,3-diaxial interactions.**)

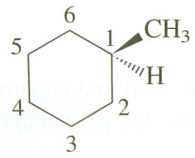
Actually, in the case of a methyl substituent, each of the 1,3-diaxial interactions is identical to the interaction between the two methyl groups in the gauche conformation of butane. The last part of Figure 6.16 shows a Newman projection down the C-1—C-2 bond of the ring. The dihedral angle between the methyl group on carbon 1 and carbon 3 is 60°, just like the dihedral angle between the methyl groups in gauche butane. The axial methyl group is also gauche to C-5, as can be seen by viewing a Newman projection down the C-1—C-6 bond. Because the gauche interaction in butane destabilizes that conformation by 0.8 kcal/mol (3.3 kJ/mol), a logical estimate for the destabilization caused by the axial methyl with its two gauche interactions is twice this value, 1.6 kcal/mol (6.6 kJ/mol). This value is in reasonable agreement with the experimental value of 1.7 kcal/mol (7.1 kJ/mol) for the **axial strain energy** for a methyl group.

PROBLEM 6.7

Draw the two chair conformations for ethylcyclohexane. Which is more stable?

The two conformations of methylcyclohexane are rapidly interconverting—they are in equilibrium. The conformer with the methyl equatorial is more stable than the conformer with the methyl axial, so the equatorial conformer is present in a larger amount in the equilibrium mixture. The axial strain energy is actually the free energy difference between the conformations and can be used to calculate the equilibrium constant for the process by using the equation $\Delta G^\circ = -RT \ln K$. Using the value of −1.7 kcal/mol (−7.1 kJ/mol) for ΔG°, the equilibrium constant is calculated to be 18 at room temperature. Therefore, at any instant, 95% of methylcyclohexane molecules have the methyl group equatorial, and only 5% have the methyl axial.

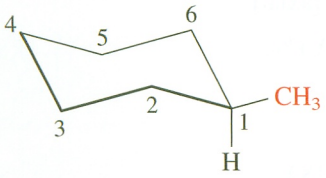
a

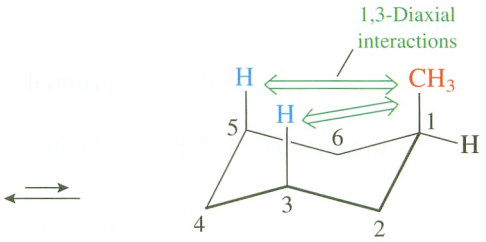


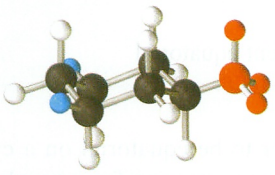
Methylcyclohexane

In diagrams like this one, which do not show conformations, the ring is pictured as lying in the plane of the page. The methyl group is above the plane in this case. Of course, the geometry of the molecule is actually a chair conformation.

b Chair Conformations







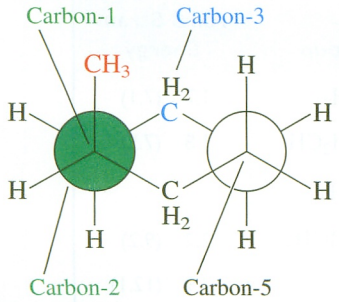
One possible chair conformation of methylcyclohexane.

The chair produced by the ring-flipping process.

It is important to be consistent in drawing chair conformations. In this book, groups that are above the plane of the page in the flat drawing are drawn closer to the top of the page in the chair conformation. The methyl group is above the page in the flat drawing, so it is closer to the top of the page than the hydrogen. In this particular drawing, the methyl group is equatorial.

Recall that ring flips interconvert all equatorial and axial groups. Therefore, the methyl group is now axial. (But note that it is still closer to the top of the page than is the hydrogen.) The steric crowding between the axial methyl and the axial hydrogens on C-3 and C-5 destabilizes this conformer. Actually, these interactions are similar to the gauche interactions in butane. This can better be seen in the Newman projection.

c Newman Projection



A Newman projection down the C-1—C-2 bond.

The methyl group on C-1 is gauche to C-3 of the ring. If a Newman projection down the C-1—C-6 bond were viewed, a similar gauche interaction between the methyl and C-5 of the ring would be found.

Figure 6.16

CONFORMATIONS OF METHYLCYCLOHEXANE. (a) FLAT RING PERSPECTIVE, (b) CHAIR CONFORMATIONS, AND (c) NEWMAN PROJECTION.

PRACTICE PROBLEM 6.3

Given that the equilibrium constant for the interconversion of the axial and equatorial conformations of methylcyclohexane is 18, show how to calculate the percentage of each that is present at equilibrium.

Solution

$$\text{axial} \rightleftharpoons \text{equatorial} \qquad K = \frac{[\text{equatorial}]}{[\text{axial}]} = 18$$

Let [equatorial] = X%, then [axial] = (100 − X) %.

$$\frac{X}{100 - X} = 18$$

$$X = 1800 - 18X$$
$$19X = 1800$$
$$X = 95\% = \text{percent equatorial}$$

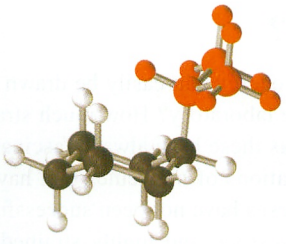
In general, substituents larger than hydrogen prefer to be equatorial on a cyclohexane ring to avoid 1,3-diaxial interactions. Axial strain energies for a number of groups are listed in Table 6.2. Note that the values for the ethyl group (1.8 kcal/mol [7.5 kJ/mol]) and isopropyl group (2.2 kcal/mol [9.2 kJ/mol]) are only slightly larger than that for the methyl group (1.7 kcal/mol [7.1 kJ/mol]), while that for the *tert*-butyl group (4.9 kcal/mol [20.5 kJ/mol]) is much larger. The ethyl and propyl groups can be rotated so that a hydrogen is pointed back over the ring to interact with the axial hydrogens, so their effective steric bulk is not much different from that of a methyl group. In contrast, the *tert*-butyl group is forced to have one of its methyl groups pointed over the ring, causing much more severe 1,3-diaxial interactions. Because of

Table 6.2 Axial Strain Energies

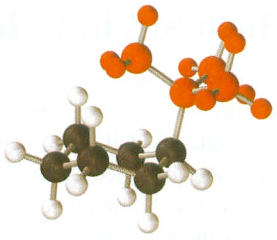
Group	Axial Strain Energy	Group	Axial Strain Energy
—C≡N	0.2 (0.8)	—CH_3	1.7 (7.1)
—F	0.25 (1.0)	—CH_2CH_3	1.8 (7.5)
—C≡CH	0.4 (1.7)	$-CH(CH_3)_2$	2.2 (9.2)
—Br	0.5 (2.1)	—Ph	2.9 (12.1)
—Cl	0.5 (2.1)	$-C(CH_3)_3$	4.9 (20.5)
—OH	0.9 (3.8)		
—NH_2	1.4 (5.9)		
—COH (O)	1.4 (5.9)		

Units are kcal/mol. Values in parentheses are in units of kJ/mol.

the resulting large axial strain energy, *tert*-butylcyclohexane exists predominantly (more than 99.9%) in the conformation with the bulky *tert*-butyl group in the equatorial position.



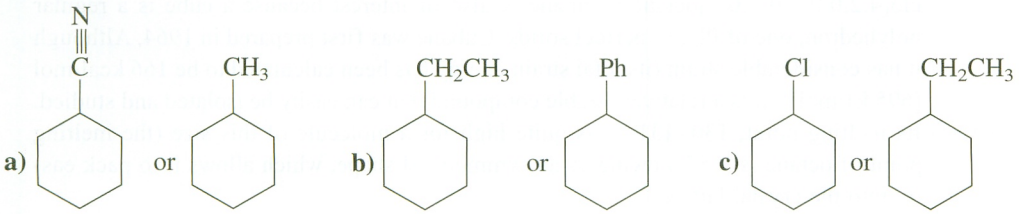
Conformation of isopropylcyclohexane with the isopropyl group axial



Conformation of *t*-butylcyclohexane with the *t*-butyl group axial

PROBLEM 6.8

Which of these compounds will have more of the conformation with the substituent on the cyclohexane ring axial present at equilibrium?



PROBLEM 6.9

Bromine is larger than chlorine, yet the two atoms have identical axial destabilization energies. Explain.

6.8 Conformations of Cyclohexanes with Two or More Substituents

The presence of two or more substituents on a ring—any size ring—introduces the possibility of stereoisomers. The existence of stereoisomers is independent of conformations and should be analyzed first because different stereoisomers will have different conformations. It is easiest to examine the stereoisomers of cyclic compounds by considering the rings to be flat, even though they may actually exist in chair or other conformations. Once all the stereoisomers have been identified, the conformations of each can be scrutinized.

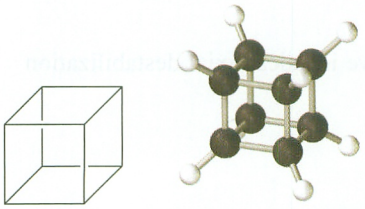
Let's begin by considering a simple disubstituted cyclohexane, 1,2-dimethylcyclohexane. If the ring is drawn flat, in the plane of the page, then one substituent on each carbon projects above the page and the other projects below the page. The situation is somewhat similar to the cis–trans isomerism that occurs with alkenes. Both

Focus On

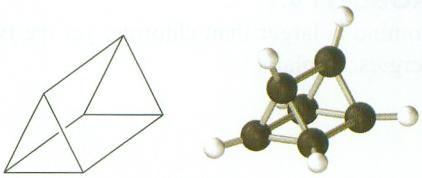
How Much Strain Is Too Much?

Molecules that would have large amounts of strain energy can easily be drawn on paper, but can they be prepared—and isolated—in the laboratory? How much strain can a molecule tolerate and still exist? Questions such as these have always fascinated organic chemists and have led them to design preparations of molecules that have very large strain energies. Although some of these syntheses have not been successful, others have led to the preparation of some very interesting, and highly strained, compounds.

For example, we know that cyclobutane has considerable strain because of its four-membered ring. How many four-membered rings can be fused together in the same molecule? A fascinating test case for this question is the molecule that has eight carbon atoms arranged in a cube, known as cubane. (This is a case in which the common name, cubane, rapidly conveys the structure of the compound and, for this reason, is more useful to even experienced chemists than is the systematic name, pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane.) Cubane is also of interest because a cube is a regular polyhedron, one of Plato's perfect solids. Cubane was first prepared in 1964. Although it has considerable strain (its total strain energy has been calculated to be 166 kcal/mol [695 kJ/mol]), it is a relatively stable compound that can easily be isolated and studied. Its melting point, 130–131°C, is quite high for a molecule of this size (the melting point of octane is −57°) owing to its symmetrical shape, which allows it to pack easily into the crystal lattice.



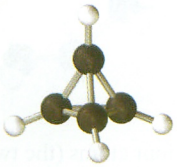
Cubane

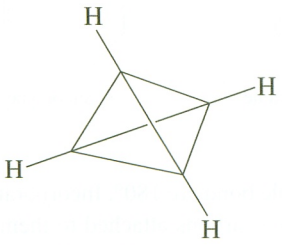


Prismane

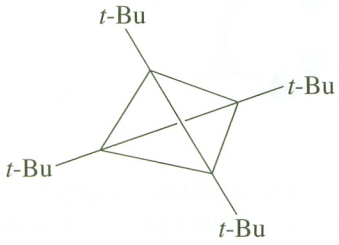
Prismane is an example of another interesting strained compound. Because it contains three-membered rings fused with four-membered rings, it should be even more strained than cubane. Prismane was prepared in 1973. It is a liquid that is stable at room temperature but explosive under some conditions. In toluene at 90°C its half-life (the time it takes for one-half of the compound to decompose) is 11 h. Note that prismane is isomeric with benzene. In fact, it was one of the structures proposed for benzene in the early days of organic chemistry.

The tetrahedron is another of Plato's perfect solids. The hydrocarbon having this shape is known as tetrahedrane. Because of its three-membered rings, it has considerably more strain than cubane and has, so far, resisted many attempts to prepare it. However, tetrahedrane substituted with *tert*-butyl groups at its vertices was prepared in 1981. It is a stable solid at room temperature.





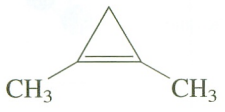
Tetrahedrane



Tetra-*tert*-butyltetrahedrane

Cyclopropane has considerable strain energy. A major part of this strain energy is due to angle strain because the 60° angles of the ring are much smaller than the tetrahedral bond angle of 109.5°. Cyclopropene should have even more angle strain because the ideal angles for a double bond are 120°. Cyclopropene was first prepared in 1960. It is quite reactive and reacts with itself at room temperature. It cannot be stored for any significant period, even at temperatures as low as −78°C. However, 1,2-dimethylcyclopropene is considerably less reactive and is stable at 0°C. The methyl groups help protect the reactive double bond by hindering the approach of other reagents. Even though the cyclopropene ring has so much strain, it does occur naturally in the fatty acid malvalic acid, a component of cottonseed oil. The reactive cyclopropene ring is thought to be one of the causes of abnormalities that develop in animals that ingest cottonseed oil.

Cyclopropene



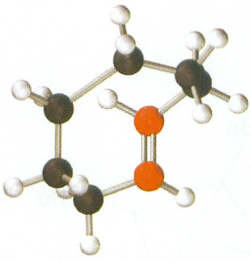
1,2-Dimethylcyclopropene

Malvalic acid

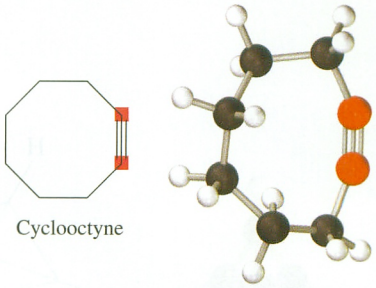
Rings of five or more carbons can accommodate a double bond without angle strain as long as that double bond is cis. However, trans double bonds are highly strained in normal-sized rings. In rings that are larger than 11 membered, the *trans*-isomer is more stable than the *cis*-isomer, as is also the case for noncyclic compounds. In rings that are 11 membered and smaller, the *cis*-isomer is more stable than the *trans*-isomer. The smallest simple *trans*-cycloalkene that has been isolated is *trans*-cyclooctene. However, even smaller examples can be generated, although their

Continued

lifetimes are very short. For example, *trans*-1-phenylcyclohexene has a lifetime of 9×10^{-6} s.

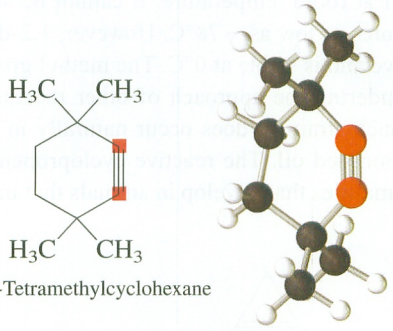


trans-Cyclooctene

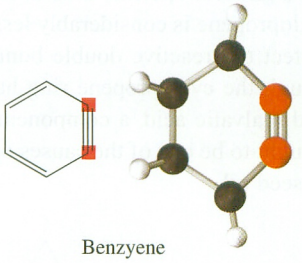


Cyclooctyne

The normal bond angles for a triple bond are 180°. Incorporating four atoms (the two carbons of the triple bond and the two carbons attached to them) into a ring in a linear manner can be accomplished only in large rings. In smaller rings the triple bond will cause considerable angle strain. The smallest cycloalkyne that has been isolated is cyclooctyne, which was prepared in 1953. Again, even smaller cycloalkynes have been generated and have a transient existence. For example, 3,3,6,6-tetramethylcyclohexyne can be prepared and studied in a frozen argon matrix at 20 K, and the presence of benzyne as a transient species in a number of reactions is well accepted (see Chapter 17).

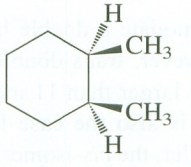


3,3,6,6-Tetramethylcyclohexane

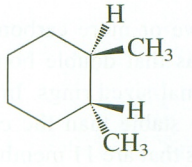


Benzyene

methyl groups can be above the plane of the ring (the *cis*-isomer), or one can be above and one can be below (the *trans*-isomer):



cis-1,2-Dimethylcyclohexane



trans-1,2-Dimethylcyclohexane

These two compounds have the same bonds but a different arrangement of these bonds in space. They are stereoisomers. Like cis–trans isomers, they cannot interconvert without breaking a bond, a process that does not occur at room temperature. Note that the same type of isomers can exist with any size ring, not just six-membered ones.

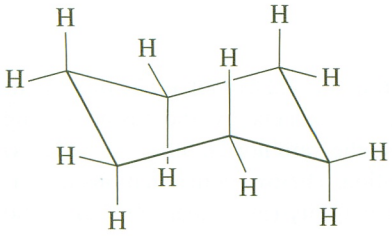
PROBLEM 6.10

Draw the stereoisomers of these compounds:

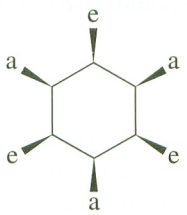
a) 1,3-Dimethylcyclohexane
b) 1,2-Diethylcyclopropane
c) 1-Chloro-3-methylcyclopentane

Let's examine the conformations of each of these stereoisomers of 1,2-dimethylcyclohexane. Those of the *cis*-isomer are shown in Figure 6.17, and those of the *trans*-isomer are shown in Figure 6.18. As can be seen in these figures, *cis*-1,2-dimethylcyclohexane exists as a mixture of two conformers, both with one axial methyl group and one equatorial methyl group and with identical strain energies of 2.5 kcal/mol (10.4 kJ/mol). The *trans*-isomer exists almost entirely in the conformation with both methyls equatorial that has a strain energy of only 0.8 kcal/mol (3.3 kJ/mol). Thus, the *trans*-isomer is more stable than the *cis*-isomer by about 1.7 kcal/mol (7.1 kJ/mol), the strain energy caused by one axial methyl group.

We must be a little cautious in generalizing these results to 1,3- and 1,4-dimethylcyclohexane. First, let's examine how the axial and equatorial positions vary as we proceed around the ring.

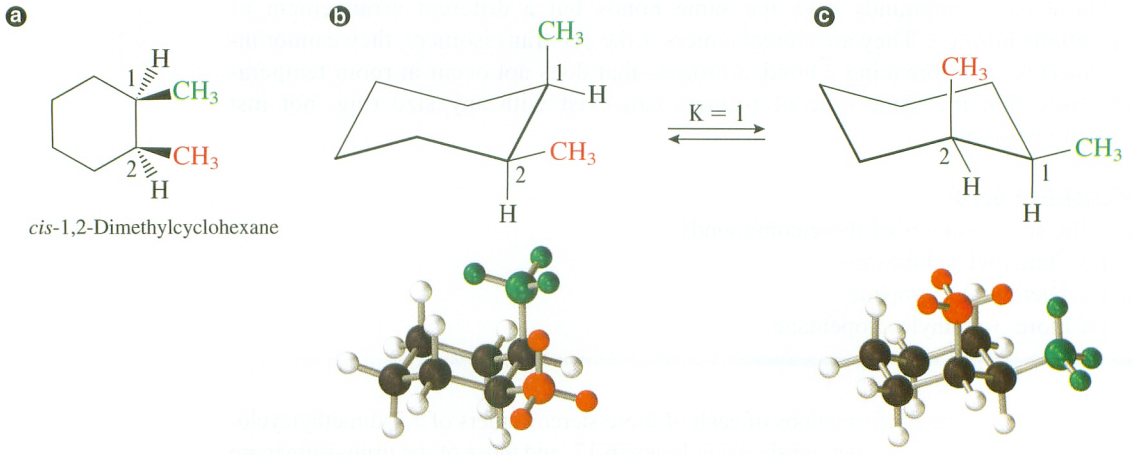


In this representation of the cyclohexane chair conformation, if the hydrogen that is closer to the top of the page is axial on one carbon, it is equatorial on the adjacent carbon. This alternation continues around the entire ring.



In this flat representation, then, the bonds above the plane of the page also alternate between being axial and being equatorial as one proceeds around the ring. Depending on which of the two chair conformations is examined, an "up" bond on a particular carbon may be either axial or equatorial. However, if the "up" bond at a particular carbon is axial, then the "up" bonds at both adjacent carbons are equatorial and vice versa.

On the basis of this understanding, we can now analyze the situation for the other dimethylcyclohexanes. First, consider the case of *cis*-1,3-dimethylcyclohexane. The two methyl groups will both be axial in one conformation (the less stable one), and they will both be equatorial in the other, more stable conformation. The total strain energy of the diaxial conformation cannot be calculated directly from the axial destabilization energies in Table 6.2. Recall that the strain energies listed in that table are for 1,3-diaxial interactions between the groups and the two axial hydrogens on the same side of the ring. However, the destabilization caused by a 1,3-diaxial interaction between two bulky methyl groups is considerably larger. Therefore, the diaxial conformation is expected to have a total strain energy that is larger than twice the destabilization energy due to one



a Both methyl groups are above the plane of the page.

b Note that both methyl groups are drawn closer to the top of the page than the hydrogens, because the methyls are both above the plane of the page in **a**. The methyl group on C-1 is axial, and the methyl group on C-2 is equatorial. The strain energy of this conformer is 1.7 kcal/mol (7.1 kJ/mol) due to the axial methyl group plus 0.8 kcal/mol (3.3 kJ/mol) due to a gauche interaction between the methyl groups, for a total of 2.5 kcal/mol (10.4 kJ/mol).

c The chair conformation produced by the ring-flipping process still has both methyl groups closer to the top of the page. The methyl group on C-1 is now equatorial, and the methyl group on C-2 is now axial. Both conformations have one axial methyl group and one equatorial methyl group, so they have identical strain energies. The equilibrium constant for the ring-flipping process is 1.0.

Figure 6.17

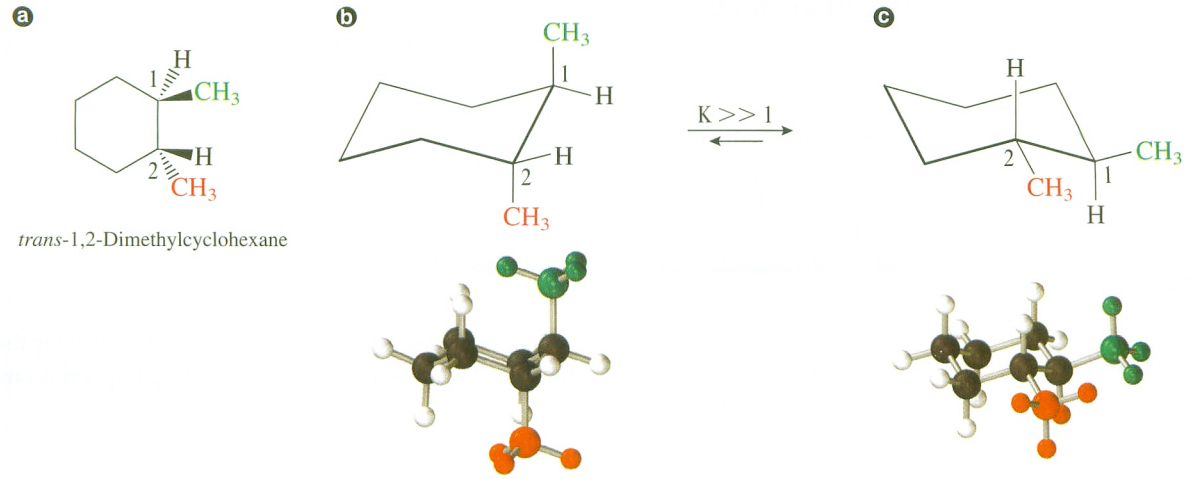
CONFORMATIONS OF *CIS*-1,2-DIMETHYLCYCLOHEXANE.

axial methyl group (greater than $2 \times 1.7 = 3.4$ kcal/mol [14.2 kJ/mol]). The other conformation, with both methyl groups equatorial, has no strain energy (there is no gauche interaction between the two methyl groups because they are not on adjacent carbons) and is much more stable than the diaxial conformation. The two conformations are interconverting rapidly, but at any one instant a vast majority (more than 99.9%) of the molecules have the conformation with both methyls equatorial because this conformation is so much more stable.

For *trans*-1,3-dimethylcyclohexane, one methyl is axial and one methyl is equatorial in either conformation. Both conformations have 1.7 kcal/mol (7.1 kJ/mol) of strain energy, and the equilibrium constant for their interconversion is 1.0. The *trans*-isomer is less stable than the *cis*-isomer by 1.7 kcal/mol (7.1 kJ/mol) because of this axial methyl group.

PRACTICE PROBLEM 6.4

Draw both chair conformations of *cis*-1,3-dimethylcyclohexane. Indicate whether each methyl group is axial or equatorial.



trans-1,2-Dimethylcyclohexane

a The methyl groups are on opposite sides of the plane of the ring.

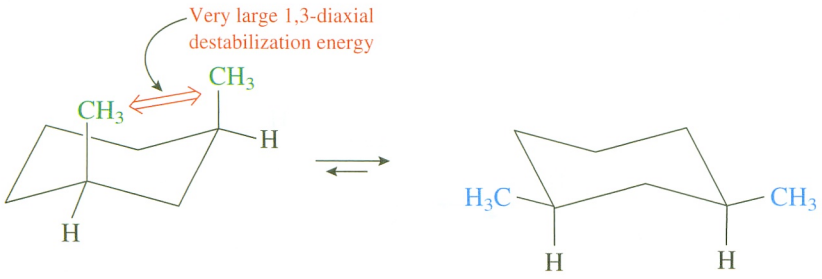
b The methyl on C-1 is closer to the top of the page, and the methyl on C-2 is closer to the bottom of the page. Both methyl groups are axial in this conformation. The strain energy due to an axial methyl is 1.7 kcal/mol (7.1 kJ/mol), so the total strain energy of this conformer is twice this value, or 3.4 kcal/mol (14.2 kJ/mol).

c The conformation produced by ring-flipping has both methyl groups equatorial and is much more stable than the other. The only strain energy present here is 0.8 kcal/mol (3.3 kJ/mol) due to a gauche interaction between the two methyl groups. Therefore, this conformer is about 2.6 kcal/mol (10.9 kJ/mol) more stable than **b**. The equilibrium is greatly in favor of **c** (>99%).

Figure 6.18

CONFORMATIONS OF *TRANS*-1,2-DIMETHYLCYCLOHEXANE.

Solution



Both methyl groups are axial.

Both methyl groups are equatorial.

PROBLEM 6.11

Draw both chair conformations of *trans*-1,3-dimethylcyclohexane. Indicate whether each methyl group is axial or equatorial.

PROBLEM 6.12

Consider the two stereoisomers of 1,4-dimethylcyclohexane.

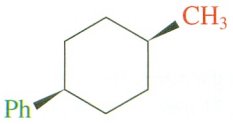
a) Explain whether each methyl is axial or equatorial in the conformations of the *cis*-isomer.

b) Explain whether each methyl is axial or equatorial in the conformations of the *trans*-isomer.

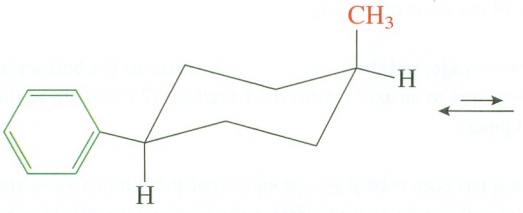
c) Explain which stereoisomer is more stable.

d) Draw the more stable conformation of the more stable stereoisomer.

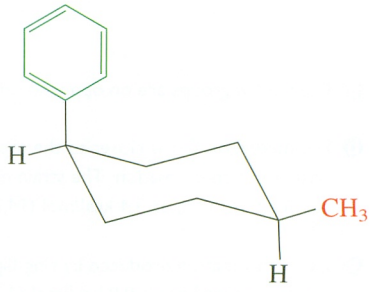
What happens if there are two nonidentical groups on the ring? Let's consider the case of 1-methyl-4-phenylcyclohexane. The *cis*-isomer will have one group axial and one group equatorial:



cis-1-Methyl-4-phenylcyclohexane



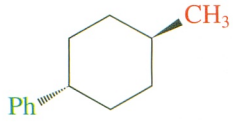
This conformation has an axial methyl and an equatorial phenyl. It has 1.7 kcal/mol (7.1 kJ/mol) of strain energy.



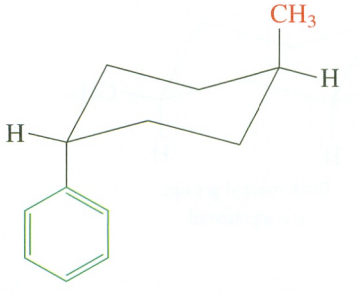
This conformation has an axial phenyl and an equatorial methyl. It has 2.9 kcal/mol (12.1 kJ/mol) of strain energy.

The axial destabilization energy (see Table 6.2) for the phenyl group (2.9 kcal/mol [12.1 kJ/mol]) is larger than that for the methyl group (1.7 kcal/mol [7.1 kJ/mol]), so the conformation with the phenyl equatorial will be more stable by 2.9 − 1.7 = 1.2 kcal/mol (5.0 kJ/mol), and it will predominate at equilibrium.

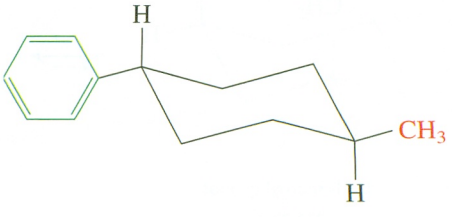
The conformations of *trans*-1-methyl-4-phenylcyclohexane have both groups equatorial or both groups axial:



trans-1-Methyl-4-phenylcyclohexane



This conformation has both groups axial. It has a total strain energy of 1.7 + 2.9 = 4.6 kcal/mol (19.2 kJ/mol).



This conformation has both groups equatorial. It has no strain energy.

The conformation with both groups equatorial is obviously much more stable than the other. Overall, the *trans*-stereoisomer is more stable than the *cis*-stereoisomer by the amount of strain due to the axial methyl group in the *cis*-isomer—that is, by 1.7 kcal/mol (7.1 kJ/mol).

Determination of the relative stability of many other substituted cyclohexane stereoisomers can be done in a similar manner. However, examples in which there are complications due to 1,3-diaxial interactions between groups or examples in which the rings are substituted with polar groups, whose dipoles interact, are much more complicated. Recently, computer programs have been developed that enable the most stable conformation of many molecules, cyclic and noncyclic, to be determined. These "molecular mechanics" calculations can provide the most stable shape of even quite complex molecules.

PROBLEM 6.13

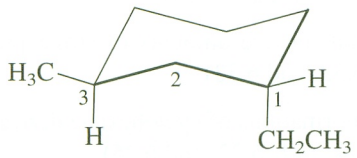
Consider the two stereoisomers of 3-isopropylcyclohexanol.

a) Which is the more stable conformation of each stereoisomer?

b) Which is the more stable stereoisomer? By how much?

PRACTICE PROBLEM 6.5

Are the substituents cis or trans in the following conformation of one of the stereoisomers of 1-ethyl-3-methylcyclohexane? Is the ethyl group axial or equatorial? Is the methyl group axial or equatorial? Which is more stable, the conformation shown or the conformation resulting from a ring-flip? Which is more stable, the compound shown or its stereoisomer?



Solution

The methyl is closer to the top of the page than the H on C-3, and the H is closer to the top of the page than the ethyl on C-1, so the ethyl is trans to the methyl. Thus, this is one chair conformation of *trans*-1-ethyl-3-methylcyclohexane. In the conformation shown, the methyl is equatorial and the ethyl is axial. The ring-flipped conformation, with the methyl axial and the ethyl equatorial, is slightly more stable (by only 0.1 kcal/mol, from Table 6.2). *cis*-1-Ethyl-3-methylcyclohexane, the stereoisomer of the compound shown, is more stable because it has a conformation in which both the ethyl and the methyl groups are equatorial.

PROBLEM 6.14

For these compounds, indicate whether the substituents are cis or trans, whether they are axial or equatorial, whether the conformation shown or the other chair conforma-

tion is more stable, and whether the compound shown or one of its stereoisomers is more stable.

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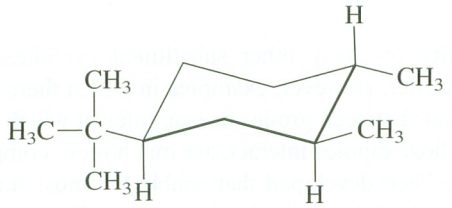
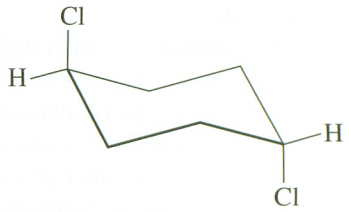
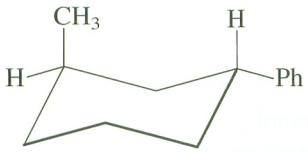
a)



b)



c)



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Review of Mastery Goals

After completing this chapter, you should be able to:

- Recognize compounds that exist as cis–trans isomers and estimate the relative stabilities of these isomers. (Problems 6.15 and 6.31)
- Use the *Z* and *E* descriptors to designate the configurations of cis–trans isomers. (Problems 6.16, 6.17, and 6.27)
- Determine the conformations about a C—C single bond and estimate their relative energies. (Problems 6.18, 6.19, and 6.29)
- Determine the types and relative amounts of strain present in cyclic molecules. (Problems 6.20, 6.30, 6.32, and 6.33)
- Draw the two chair conformations of cyclohexane derivatives and determine which is more stable. (Problems 6.21, 6.22, and 6.25)
- Use analysis of conformations to determine the relative stabilities of stereoisomeric cyclohexane derivatives. (Problems 6.23, 6.24, and 6.26)

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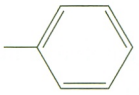
Additional Problems

6.15 Draw all the cis–trans isomers for these compounds:

a) $CH_3CH{=}CHCH{=}CHCH_2CH_3$ **b)** $CH_3CH{=}CHCH{=}CHCH_3$

c) $CH_3CH{=}CHCH{=}CH_2$

6.16 Which of these groups has the higher priority?

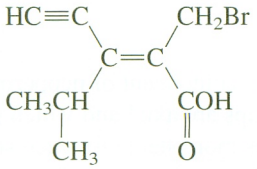
a) $-C{\equiv}CH$ or 

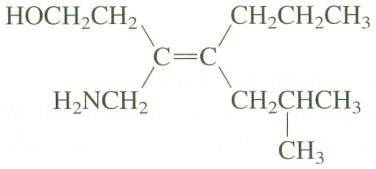
b) $-C{\equiv}N$ or $-CH_2\underset{\displaystyle Br}{\underset{|}{C}}H_2$

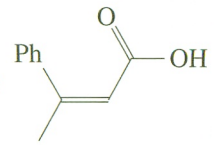
c) $-\underset{\displaystyle H}{\underset{|}{C}}{=}CH_2$ or $-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$

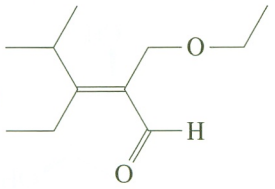
d) $-C{\equiv}CH$ or $-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$

6.17 Assign the configurations of these compounds as *Z* or *E*:

a) 

b) 

c) 

d) 

6.18 How would the energy versus dihedral angle plot for 2-methylpropane (isobutane) differ from that for propane?

6.19 Draw an energy versus dihedral angle plot for the conformations of 2,3-dimethylbutane about the C-2—C-3 bond.

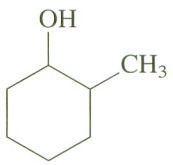
6.20 Discuss the geometry and the types of strain present in these compounds:

a) Cyclopropane **b)** Cyclobutane
c) Cyclopentane **d)** Cyclohexane
e) Cyclodecane

6.21 Explain why the axial strain energies for the $-C{\equiv}N$ group and the $-C{\equiv}CH$ group are much smaller than that for the CH_3 group.

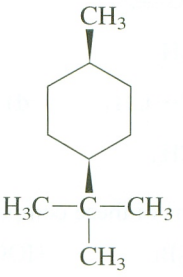
6.22 Draw the chair conformations of 1,1,3-trimethylcyclohexane. Which conformation is more stable? Why is it not possible, on the basis of the material in this chapter, to determine the exact energy difference between these conformations?

6.23 Draw the cis and trans stereoisomers of this compound and explain their relative stabilities.



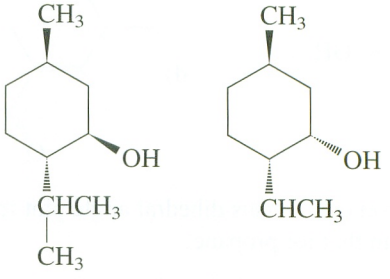
6.24 Draw both chair conformations of 1-methyl-1-phenylcyclohexane. Which is more stable? By how much energy?

6.25 Explain whether the methyl is axial or equatorial in this compound:



BioLink

6.26 Draw both chair conformations for menthol (a component of peppermint oil) and its stereoisomer, neomenthol. Which groups are axial and which groups are equatorial? Explain which conformation is more stable for each stereoisomer. Which stereoisomer is more stable? By how much energy?



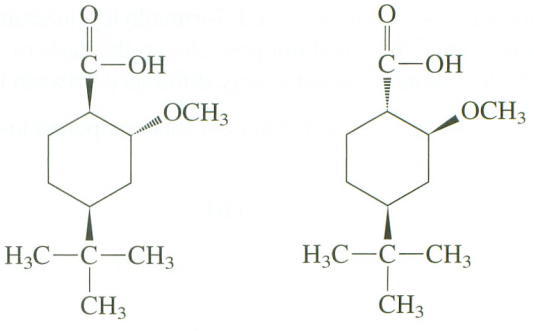
Menthol Neomenthol

6.27 Draw the structures of these compounds.

a) (*E*)-3-Hexene

b) (*Z*)-2-Chloro-3-isopropyl-2-heptene

6.28 Which of these compounds can form an intramolecular (within the same molecule) hydrogen bond between the hydrogen of the carboxylic acid and the oxygen of the ether group? Explain. (*Hint:* Construct models.)

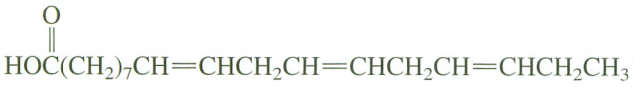


6.29 Draw Newman projections for the anti and gauche conformations about the C—C bond of these compounds. What other factors, besides steric and torsional strain, influence the stability of these conformations?
a) 1,2-Dichloroethane **b)** 1,2-Ethanediol

6.30 Explain which is more stable, *cis*-1,2-dimethylcyclopropane or *trans*-1,2-dimethylcyclopropane.

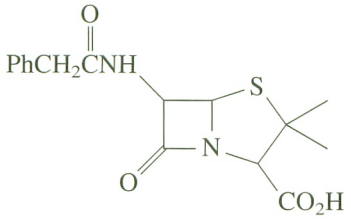
6.31 Linoleic acid and α-linolenic acid are two naturally occurring unsaturated fatty acids that are components of fats. Explain how many cis–trans isomers exist for each of these fatty acids. Interestingly, only the all-cis isomers of each occur naturally. Draw the structure of the naturally occurring stereoisomer of linoleic and α-linolenic acid using skeletal structures.

Linoleic acid



α-Linolenic acid

6.32 Penicillins are relatively unstable compounds and are usually stored in a refrigerator for this reason. Suggest a factor that contributes to the reactivity of penicillin G.



Penicillin G

6.33 Build a handheld model of bicyclo[2.2.1]heptane and discuss the types of strain that are present in this compound.

Bicyclo[2.2.1]heptane

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6.34 Explain whether the compound shown is the *Z* or the *E* diastereomer.

6.35 Explain whether the conformation shown is the most stable conformation of each of these molecules.

6.36 Explain which stereoisomer is more stable.

6.37 Explain which isomer has more strain energy in the conformation shown.

6.38 For these compounds, indicate whether the substituents are cis or trans, whether they are axial or equatorial, whether the conformation shown or the other chair conformation is more stable, and whether the compound shown or one of its stereoisomers is more stable.

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